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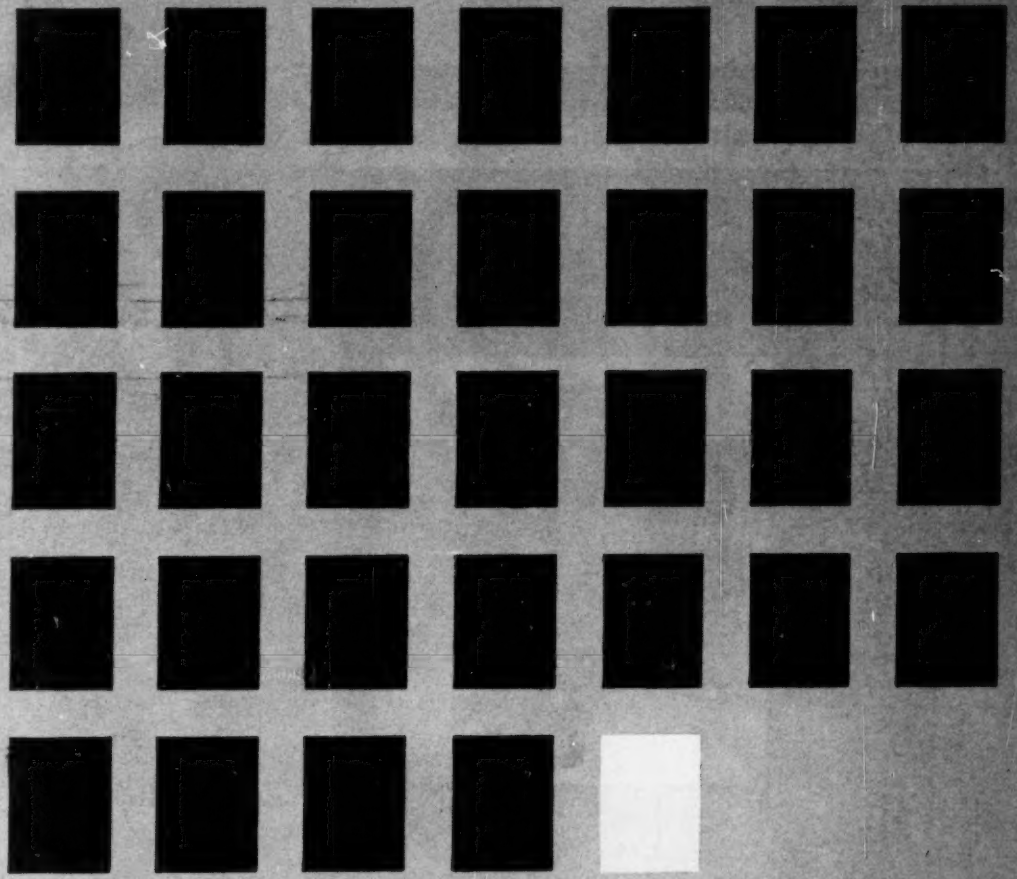

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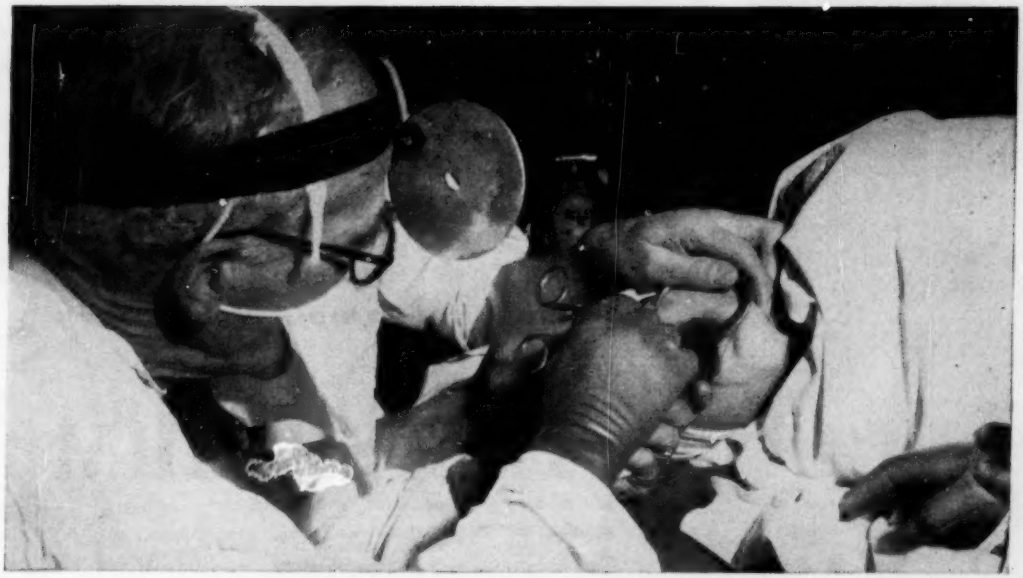

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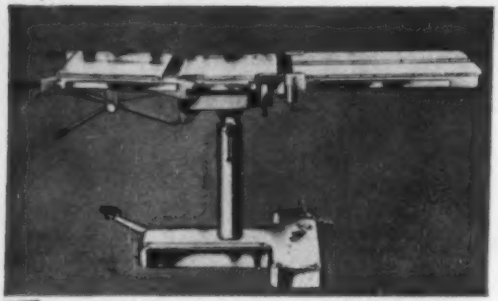

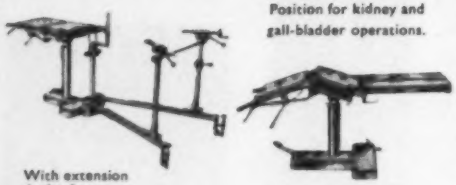

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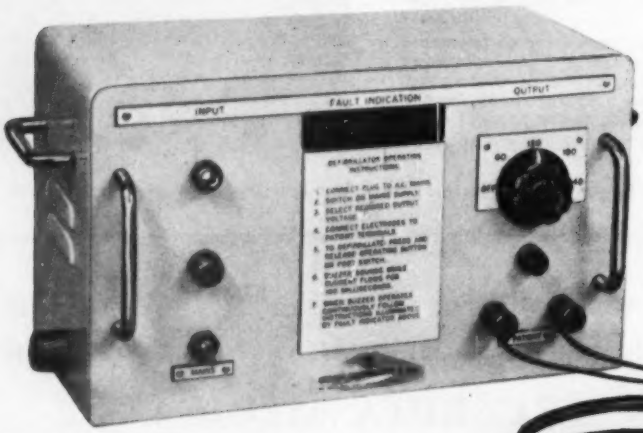

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BRITISH JOURNAL OF ANAESTHESIA

VOL. XXXII, No. 12 DECEMBER 1960

EDITORIAL

THE REPRESENTATION OF ANAESTHETISTS

At a recent meeting of the British Medical Association Anaesthetists' Group Committee, it was reported that only one new member had been enrolled during the last twelve months. It is true that there are already nearly eight hundred members of this Group but an even larger membership would be welcome. Those who have not up to now joined the British Medical Association Group should do so. It entails no expense to members of the British Medical Association.

Anaesthetists are also represented by their own Association and their Faculty within the Royal College of Surgeons. Each one of these bodies has contributed very significantly to the progress of anaesthesia, that is directly to the well-being of the patients, and also, of course, to the present status of anaesthetists.

It should not be necessary to state that all British anaesthetists should be Fellows or Members of the Association of Anaesthetists of Great Britain and Ireland, if for no other reason than that to a considerable measure they owe to the activities of this Association their present status and position; furthermore, the Association has research and educational funds readily available to its members. It must not be forgotten that this, of the three representative groups, is the only one which can give independent advice. On the other hand the Faculty and the B.M.A. Group have more direct access to the Ministry of Health through the regular negotiating machinery.

It is extremely important that all three should be fully supported.

BERNARD JOHNSON MEMORIAL FUND

We would like to draw the attention of our readers to the letter from the Dean of the Faculty which appears on page 619.

It will be seen from this that an anonymous donor has offered to double any donations to the Bernard Johnson Memorial Fund *raised between January* 1 *and the date on which the appeal closes,* up to a maximum donation by this benefactor of £250. We have pointed out before how much anaesthesia in this country owes to the late Dr. Bernard Johnson and we appeal again to all to contribute. It will be remembered that the fund is for the establishment of a Bernard Johnson Memorial Postgraduate Tutor in the Faculty of Anaesthesia in the Royal College of Surgeons, and for the erection of a suitably inscribed plaque over the laboratories of the Research Department in the College.

Brit. J. Anaesth. (1960), **32**, 566

THE EFFECT OF METHYLATION ON THE ANAESTHETIC ACTION OF ETHYL-METHYL-PROPYL-THIOBARBITURATE

BY

JOHN W. DUNDEE, DAVID W. BARRON, AND ROBIN KING

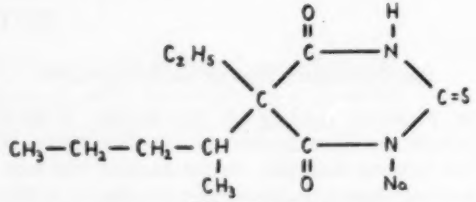
Department of Anaesthetics, Queen's University of Belfast, Northern Ireland

THE opportunity of studying the relationship of chemical structure to clinical action of drugs rarely presents itself to the practising anaesthetist, particularly with regard to intravenous drugs. Such studies are not only useful from the clinical point of view but they may provide valuable information to the research chemist, by indicating possible lines of approach to the development of other new compounds. The closely related compounds which are commercially available, for example thiopentone and thiamylal or thialbarbitone, are so similar in their clinical action that it would be difficult to distinguish them under operating theatre conditions.

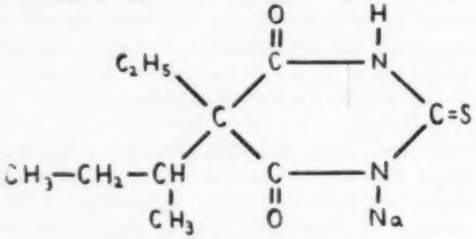
The authors have been fortunate in that they recently have had access to supplies of two thiobarbiturates which differ only in the addition of a N-methylated side chain. One of these compounds is the German drug, inactin, the first use of which in this country has recently been described by Dundee and Riding (1960). The other drug is known as B.137 and its pharmacology has been reported by Peel and his colleagues (1959). A preliminary report of its anaesthetic properties in man and a comparison of its action with those of thiopentone has been produced by the authors (Barron, Dundee and King, 1960).

The chemical structure of thiopentone, inactin and B.137 is shown in figure 1. The physical properties of all three drugs are similar and each is buffered with 6 per cent (W/W) sodium carbonate. The pH of solutions, prepared as near as possible under clinical conditions, is given in table I.

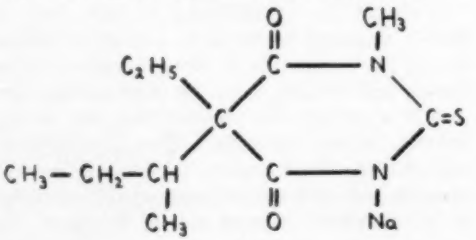
While the prime object of this study was a comparison of the effects of B.137 and inactin, thiopentone was included since it is the standard drug used in this country. This will help readers to appreciate the clinical implications of the findings.



Thiopentone
Sodium 5-ethyl-5′-(1-methylbutyl)-2-thiobarbiturate.



Inactin
Sodium 5-ethyl-5′-(1-methylpropyl)-2-thiobarbiturate.



B.137
Sodium 1-methyl-5-ethyl-5′-1(-methylpropyl)-2-thiobarbiturate.

FIG. 1
Formulae of the three thiobarbiturates.

METHOD OF STUDY

The main data to be presented in this paper were obtained with anaesthetic techniques which are based on the use of thiobarbiturates (in 5 per cent

TABLE I

pH of aqueous solutions of the three barbiturates, prepared under conditions similar to those for their clinical use. Estimations were made at laboratory temperature (67°F, 19°C), which is similar to that in operating theatres

Drug	Strength of solution (W/V)	
	2·5%	5%
Thiopentone	10·81	10·81
B.137	11·25	11·30
Inactin	10·50	10·50

solution) as main narcotic drugs. These consist of their use (*a*) with nitrous oxide-oxygen for the operation of dilatation and curettage, and (*b*) followed by suxamethonium for electroconvulsive therapy. In the first series there was no selection as to which drug was given to a patient, but in those undergoing electroconvulsive therapy an attempt was made to ensure that, as far as possible, each patient received all three drugs in random order. Unfortunately, owing to termination of treatment this was not always possible. In a further small series, B.137 was used as an induction agent for general surgical cases in which a variety of nonrelaxant anaesthetic techniques were employed.

Selection of cases.

All patients in this study were of class 1 or 2 physical status according to the classification of the American Society of Anesthesiologists. This excludes all persons exhibiting severe systemic disturbance which seriously interferes with their normal activities.

Pre-anaesthetic medication.

Because of an observation by Dundee and Riding (1960) that the addition of opiates to the premedication significantly reduces the incidence of side effects during the induction of anaesthesia with thiopentone and inactin, it was necessary to consider separately those patients who received atropine only and those who were given an opiate in addition. The dose of atropine administered prior to electroconvulsive therapy was 0.85 mg (1/75 grain) and in all other patients 0.65 mg (1/100 grain) was used. Morphine 10 mg (1/6 grain), papaveretum 20 mg (1/3 grain) and pethidine 50 to 100 mg, were the opiates used and all premedicant drugs were given parenterally about 1 hour before operation.

Recording of data.

All relevant data was recorded on forms which were specially designed for the purpose. These listed all common side effects of the drugs and their use ensured full documentation of each case.

Presentation of data.

With the exception of cardiovascular effects (which it was possible to classify according to their severity), the data to be presented are based on the presence or absence of certain side effects which follow the induction of anaesthesia. These have been grouped into those which may be assumed to be due to the excitatory properties of the thiobarbiturates (tendencies towards convulsive activity) and those which primarily affect the respiratory system. Marked respiratory depression was taken as apnoea or depression of such duration that active measures were needed to maintain oxygenation. For the sake of clarity the percentage incidence of side effects will frequently be presented, but all statistical calculations were made on absolute numbers of cases. With the exception of dosage studies the chi-squared method of analysis was used throughout. An overall assessment of the grade of induction of anaesthesia was made in each patient (excluding those undergoing electroconvulsive therapy) according to the criteria set out by Dundee and Riding (1960).

For the sake of simplicity all doses of drugs have been converted to mg/kg body weight and mean figures only are given. Studies of induction and total dosage and need for supplementation during anaesthesia are limited to those patients having minor gynaecological procedures. It was felt that no benefit would be derived from an analysis of dosage in the patients undergoing general surgical and thoracic procedures.

Sequelae of anaesthesia.

Observations of these were limited to those patients undergoing dilatation and curettage. At the end of operation these patients breathed pure oxygen for exactly 1 minute and after 1 further minute their condition was assessed as either awake, safe (presence of protective reflexes) or unsafe (indicating that a pharyngeal airway was required). Observations on postoperative emesis were all made within the first 6 hours after operation and no distinction was made between

the occurrence of nausea alone and nausea and vomiting. Patients were seen 24 to 48 hours after operation and were examined by one of us for the presence of thrombosis in the vein used for the injection.

RESULTS AND ANALYSIS OF FINDINGS

Details of the gynaecological patients which form the main part of this study are given in table II. It can be seen that the observations are based on comparable groups of patients.

Dosage.

The average induction and total doses of drugs used during the operation of dilatation and curettage are shown in table II. An analysis of this data (table III) reveals that the average induction dose of thiopentone was significantly less than that of B.137 but there was no difference between that of B.137 and inactin. The incidence of the need for supplementary dosage during this operation can be seen to be greater with B.137 than with the other two drugs. The significance of this observation will be discussed in detail later.

TABLE II

Physical characteristics of patients and average induction and total dosage of drugs used for the operation of dilatation and curettage

Pre-operative medication	Atropine			Opiate + atropine		
Drug	Thiop.	B.137	Inactin	Thiop.	B.137	Inactin
No. of patients	95	61	85	112	39	33
Average age	34·7	32·1	34·5	30·5	32·2	34·0
± (S.E.)	0·9	1·0	1·2	2·6	1·4	1·7
Average weight (kg)	60·5	61·7	60·0	61·2	60·0	60·0
± (S.E.)	1·2	1·1	1·1	1·1	2·4	0·5
Average dosage mg/kg						
Induction	5·56	6·99	6·97	5·93	7·12	6·49
± (S.E.)	0·18	0·32	0·30	0·14	0·37	0·24
Total	6·42	8·65	8·16	7·35	9·75	7·48
± (S.E.)	0·18	0·35	0·31	0·24	0·41	0·33
Percentage incidence for need of supplementary dose	47	59	55	36	68	33

TABLE III

Significance of difference between average induction doses of B.137 *and the other two thiobarbiturates*

Drug	Pre-med	t	p
Thiopentone	Atropine	3·88	<0·001
	Opiate	3·02	<0·01
Inactin	Atropine	0·005	>0·90
	Opiate	1·34	>0·10

Induction complications.

The percentage incidence of side effects (other than those pertaining to the cardiovascular system) in the same series is shown in table IV, which also includes observations made at the end of anaesthesia and the incidence of sequelae. It can be seen from this table that a high incidence of spontaneous abnormal muscle movements is a feature of anaesthesia with B.137, as compared with the other two drugs.

In patients who received atropine as sole pre-anaesthetic medication the incidence of excitatory side effects was significantly greater ($P<0.001$) with B.137 than that observed with either thiopentone or inactin. Where an opiate was given before anaesthesia the number of patients who showed no excitatory side effects was significantly greater following thiopentone ($\chi^2=15.25$, $P<0.01$) and inactin ($\chi^2=5.25$, $P<0.05$) than with B.137. With neither of the premedications was there a significant difference between the incidence of side effects which followed thiopentone and inactin.

The incidence of tremors was not significantly less with opiate premedication in B.137 cases ($\chi^2=1.46$, $0.30>P>0.20$) although muscle movements were less frequent in the opiate series ($\chi^2=13.70$, $P<0.001$) and the number of

TABLE IV

Summary of incidence of complications during induction of anaesthesia and condition of patients after end of operation

Pre-operative medication	Atropine			Opiate + atropine		
Drug	Thiop.	B.137	Inactin	Thiop.	B.137	Inactin
Percentage incidence of side effects						
(*a*) Excitatory phenomena						
Tremor	4	34	6	3	23	3
Spontaneous movements	1	61	9	6	23	9
Nil	96	30	87	93	67	91
(*b*) Respiratory upset						
Cough/hiccough	7	10	8	3	8	2
Laryngospasm	1	8	1	1	3	6
Nil	92	87	92	96	92	94
(*c*) Marked respiratory depression	4	21	2	6	27	3
Condition of patient 2 minutes after end of operation Percentage incidence						
Awake	69	43	75	56	37	—
Safe	24	40	21	35	23	—
Unsafe	7	17	4	9	40	—
Percentage incidence of sequelae						
Nausea and vomiting	7	12	—	12	31	—
Venous thrombosis*	12	24	9	—	—	—

* Data from opiate and non-opiate cases pooled

patients showing no excitatory phenomena is much less after opiate premedication (26/39) than in those receiving atropine alone (18/61). This difference is highly significant ($\chi^2=27.95$, $P<0.001$).

Irrespective of pre-anaesthetic medication there was no significant difference between the incidence of coughing, hiccough or laryngospasm with any of the three drugs.

The incidence of marked respiratory depression with the three drugs cannot be analyzed with the conventional χ^2 test, but the figures in table IV suggest that, in the dosage used, B.137 produces a greater respiratory depression than either thiopentone or inactin.

Data of patients on whom the drugs under study were used to mitigate the effects of electroconvulsive therapy are given in table V and reveal that the three series of cases are comparable. The marked similarity of the physical characteristics of the three groups of subjects is due to the large number of patients who received all three drugs. It can be seen that in this series also there was a higher incidence of excitatory phenomena after B.137 than following thiopentone or inactin. Although this difference is statistically significant ($P<0.05$), it is much less than that recorded in table III.

For obvious reasons there were no respiratory data in this group of cases.

The incidence of complications which followed the use of the thiobarbiturates for general surgical cases is shown in table VI. Although these findings have not been subjected to statistical analysis it can be seen that they conform to the pattern which is evident in the other two series. This table is included for the sole purpose of demonstrating that the undesirable effects of B.137, as shown in tables IV and V are not related to its use as sole narcotic agent.

Cardiovascular effects.

The incidence, severity and duration of hypotension in patients undergoing dilatation and curettage are shown in table VII. It was not possible to take repeated blood pressure readings in all cases.

TABLE V

Details of patients receiving electroconvulsive therapy and complications of anaesthesia resulting from the three thiobarbiturates

Thiobarbiturate	Thiop.	B.137	Inactin
No. of patients	124	81	61
Females	79	52	47
Males	45	29	14
Average age (years)	45·1	45·0	44·2
Average weight (kg)	63·8	63·8	62·7
Average dose of drug (mg/kg)	3·27 ± 0·07	3·70 ± 0·09	3·48 ± 0·20
Complications of induction			
Tremor	0	17	4
Spontaneous movement	5	6	3
Nil	109 (96%)	59 (73%)	54 (89%)

TABLE VI

Observations made during the induction of anaesthesia when the three thiobarbiturates were used in general surgical cases

Premedication	Atropine only			Opiate		
Drug	Thiop.	B.137	Inactin	Thiop.	B.137	Inactin
No. of cases	268	48	195	431	45	266
Excitatory phenomena (%)						
Tremor	2·6	45·8	6·7	1·2	20·0	2·6
Muscle movements	7·1	56·3	10·3	3·7	24·4	4·5
Nil	91·0	27·1	84·0	96·1	71·1	94·4
Respiratory upset (%)						
Cough/hiccough	3·7	12·5	7·7	1·9	4·4	4·5
Laryngospasm	1·5	4·3	1·5	0·2	0	3·4
Nil	95·1	85·4	91·8	98·1	95·6	94·7

TABLE VII

Cardiovascular effects of the induction of anaesthesia

Drug	Premedication	No. of cases	No. B.P. fall ± 20 mm Hg	Blood pressure fall		
				20 mm +	40 mm +	Recovery longer than 5 minutes
Thiopentone	Atropine	82	67 (82%)	15	1	7 (9%)
	Opiate	92	70 (76%)	22	3	9 (10%)
B.137	Atropine	48	36 (75%)	12	0	5 (10%)
	Opiate	31	18 (58%)	13	1	7 (23%)
Inactin	Atropine	60	57 (95%)	3	0	2 (3%)
	Opiate	28	16 (57%)	12	0	8 (29%)

The data given in this table refer solely to changes observed following the induction dose of the drugs. In the atropine series there was a similar incidence of patients who did not exhibit marked degree of hypotension (fall in systolic pressure up to 20 mm Hg) with the three drugs. Paucity of cases precluded the making of a reliable comparison between the effects of the individual drugs in those patients who received an opiate as pre-anaesthetic medication. However, with B.137 and inactin, there is both a higher incidence and a greater duration of hypotension when an opiate is given prior to induction of anaesthesia than when atropine alone is administered.

The maximum changes in pulse rate observed during the first 5 minutes following the induction of anaesthesia are shown diagrammatically in figure 2. This figure is based on all the dilatation and curettage cases. It demonstrates that B.137 has a greater tendency to produce an increase in pulse rate than the other two drugs, irrespective of pre-anaesthetic medication. This must be associated with the higher incidence of stormy induction of anaesthesia with B.137 and in a few instances the degree of tachycardia which followed its use was alarming.

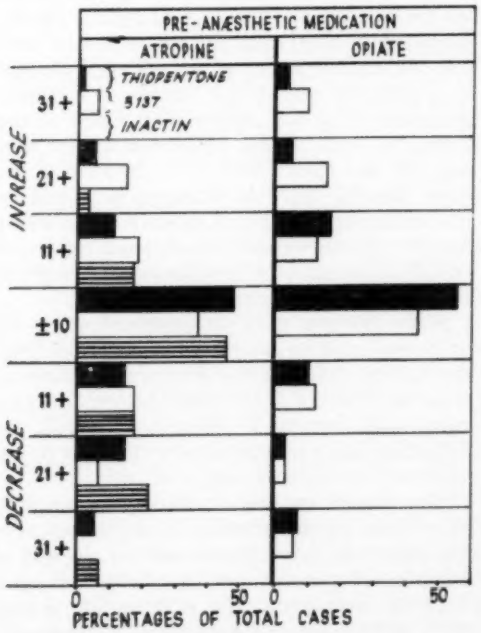


FIG. 2

Incidence of changes in heart rate following induction of anaesthesia with the three thiobarbiturates in gynaecological patients.

It will be noticed in figure 2 that, with thiopentone and inactin, the overall tendency is towards a reduction in heart rate in patients who were premedicated with atropine alone. It can be seen from table VIII that differences in the mean pre-induction heart rate were not the cause of the changes noted above.

TABLE VIII

Mean absolute pulse rates before and after the use of induction doses of the three thiobarbiturates in dilatation and curettage patients

Premedication	Drug	Before induction	After induction 5 min	After induction 10 min
Atropine	Thiopentone	100·3	98·0	93·9
	B.137	101·6	106·1	100·8
	Inactin	105·7	103·5	96·6
Opiate	Thiopentone	83·3	85·8	83·9
	B.137	87·0	96·1	88·7

Recovery from anaesthesia.

The only comparable data on this aspect of the action of the three drugs is that presented in table IV. It would appear from this that, with the doses shown in table II, B.137 offers no advantages over other drugs as regards rapidity of return of consciousness.

The incidence of nausea and vomiting following dilatation and curettage was not observed in the inactin patients, but can be seen to be greater following B.137 than after thiopentone, irrespective of pre-anaesthetic medication. With both of these drugs the addition of an opiate to the premedication increased the incidence of nausea and vomiting.

Local effects.

Venous thrombosis was a troublesome complication following the use of a 5 per cent solution of B.137. Not only is the incidence much greater than that after thiopentone and inactin used in the same concentration of solution (table IV), but the extent of the thrombosis was often alarming following the injection of the methylated compound.

Grade of anaesthesia.

The induction of anaesthesia was graded according to the scheme described by Dundee and Riding (1960) so as to allow for an overall evaluation of the action of the three drugs. The absence of any complications during the induction is graded as 1, while in grade 3 the patient's life is either placed in jeopardy by the anaesthesia or conditions are such that surgery is completely impossible. The data in figure 3 were obtained from the patients undergoing minor gynaecological surgery and, for simplicity, only the incidence of grades 1 and 3 are shown. This leaves little doubt as to the unsuitability of B.137 as an induction agent in the absence of opiate premedication. Even when a pre-operative dose of opiate is given, the results with B.137 are less satisfactory than with the other two thiobarbiturates.

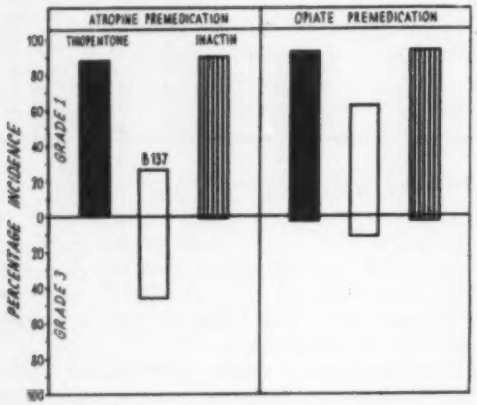


FIG. 3

Incidence of grades 1 and 3 anaesthesia in the gynaecological series of patients.

Other data.

The authors initially formed the impression that the onset of anaesthesia with B.137 was slower than with the other two drugs. It was felt that this might be attributable to undue caution with the use of a new agent and hence the onset time was measured using the technique previously described with inactin (Dundee and Riding, 1960).

Reactive hyperaemia was produced in the forearm by the release of an arterial tourniquet which had been applied for 2½ minutes. Fifteen seconds later a predetermined dose of B137 was injected into a vein in the antecubital fossa over a period of 5 seconds. The patient was instructed to count and the time was measured from the end of injection to the cessation of counting. The dose was varied so as to cover the range of from 2 to 8 mg/kg body weight.

In figure 4 the findings with B.137 are compared with those obtained with thiopentone in a previous study. It can be seen that this drug is capable of producing sleep within one arm-brain circulation time. The minimum dose with which this effect can be consistently produced is slightly greater than that for thiopentone, and in this respect it resembles inactin.

DISCUSSION

These findings confirm those of Dundee and Riding (1960) that, in equipotent doses, the clinical effects of thiopentone and inactin are comparable. They also show that N-methylation of the latter drug produces a compound which can have no place in clinical anaesthesia. Nevertheless, it is interesting and instructive to consider the clinical effects of this chemical change. It is generally agreed that inactin is a slightly less potent drug than thiopentone. Based on the findings in table II and figure 3 it can be seen that this also applies to B.137. The ratio of the mean dose of B.137 is compared with that of thiopentone and inactin in table IX. This shows that the potency of the N-methylated compound (B.137) is not different from the parent compound (inactin).

From previous work on modifications of the barbiturate nucleus (Maynert and van Dyke, 1949) it would be expected that a more rapid recovery from the effects of B.137 would be noted as compared with inactin. In support of this is the higher incidence of need of supplementary dosage with the N-methylated compound (table II) and the higher ratio of the total to induction dose (table IX). However, this evidence is misleading since the percentage of patients awake at the end of the standard operation was lower with B.137 than with the other two drugs. It is feasible to consider that the large and frequent supplementary doses were given in an attempt to control undesirable spontaneous involuntary muscle movement which was a feature of anaesthesia with B.137

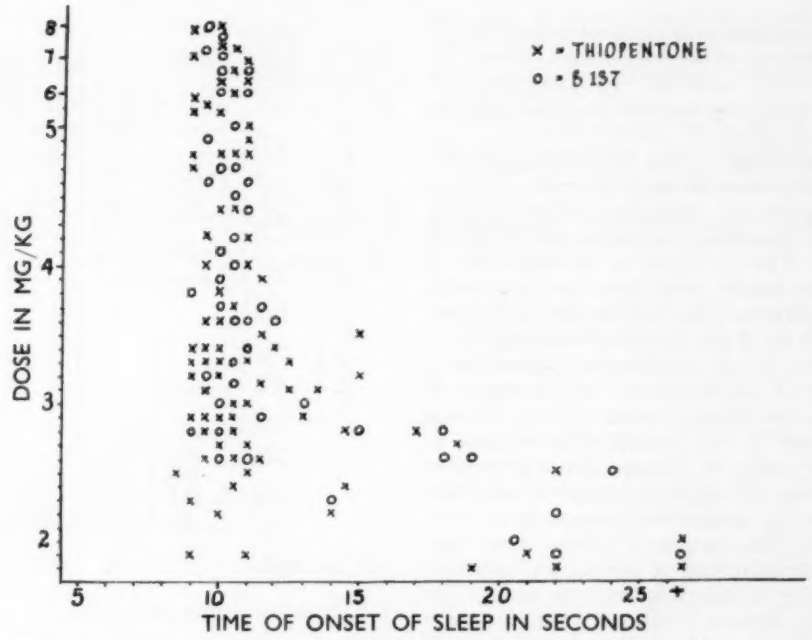


FIG. 4

Relationship between dose and time from end of injection to loss of consciousness with B.137 and thiopentone.

TABLE IX

Ratio of mean induction and total doses of B.137 to that of the other thiobarbiturates, and of mean total to induction doses of all three drugs

Dose	Drugs	Premedication	
		Atropine	Opiate
Mean induction	Thiopentone/B.137	0·79	0·83
	Inactin/B.137	1·00	0·91
Mean total	Thiopentone/B.137	0·74	0·77
	Inactin/B.137	0·94	0·76
Ratio of total to induction	Thiopentone	1·15	1·24
	B.137	1·24	1·37
	Inactin	1·17	1·15

TABLE X

Relationship between need for supplementary dosage and presence or absence of excitatory side effects. This relationship is not statistically significant

Presence of excitatory side effects	Need for supplementary dosage		
	+	—	Total
+	40	16	56
—	25	19	44
Total	65	35	100

($\chi^2 = 3{\cdot}064$; df = 1 ; $0{\cdot}10 > P > 0{\cdot}05$)

and this hypothesis is examined in table X. Although the relationship studied in this table was not statistically significant, it is highly suggestive and the findings might have been different had the subjects who required a short acting relaxant to control the movements, which followed the B.137, been excluded. Unfortunately, this was not possible in a retrospective examination of our data. It was not our clinical impression that recovery from uneventful B.137 anaesthesia was more rapid than from inactin or thiopentone.

The most outstanding effect of methylation on the action of inactin is the production of a high incidence of spontaneous abnormal muscle movements. This complication has been noted with other N-methylated barbiturates, particularly hexobarbitone, but the frequency and severity is not nearly as great as that encountered in this

study. The mitigation of these side effects by the pre-operative use of an opiate (tables IV and VI) has also been observed with hexobarbitone (Dundee, 1956), but the effects are less striking than with B.137.

It is interesting to note that Stoelting (1953) did not find excitatory side effects as a feature of the action of methylated thiobarbiturates (including N-methyl thiopentone and N-methyl thiamylal). This is contrary to the experience of one of the authors with these two compounds and this difference may well be due to the pre-anaesthetic use of the opiates in Stoelting's series.

That this is not the complete explanation is shown by a comparison of the incidence of excitatory side effects in tables IV and VI with that in table V. The average induction dose in the latter series of patients (electroconvulsive therapy) was 3.7 mg/kg as compared with 6.99 mg/kg in the comparable gynaecological series (table IV). This increase in dosage more than doubled the percentage of patients who exhibited one or other of the excitatory phenomena. The relationship between induction dose and incidence of side effects is strikingly illustrated in figure 5. This is based on the pooled data of all the cases in this study. It can also be seen that this relationship is more striking in patients who have not received a pre-anaesthetic injection of an opiate.

One of the baffling features of anaesthesia with B.137 was the failure of increasing doses to control muscle movements. That the magnitude of the induction dose played a part in the incidence and severity of these side effects was not appreciated until nearly the end of this study and the high incidence of tachycardia observed with B.137 may be related to the use of very large doses in patients in a near-convulsive state.

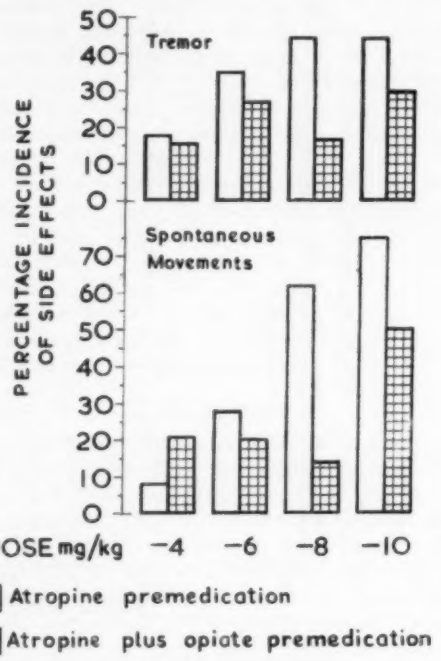


FIG. 5
Percentage incidence of excitatory side effects related to the induction dose of B.137.

SUMMARY AND CONCLUSIONS

B.137, the N-methylated form of sodium ethyl-methyl-propyl-thiobarbiturate has been compared with its nonmethylated analogue, inactin, and with thiopentone. All three compounds produce loss of consciousness in the arm-brain circulation time.

Methylation does not appear to alter the potency of inactin, which is slightly less than that of thiopentone. The authors were unable to substantiate the claim that N-methylation resulted in a more rapid return of consciousness, but it markedly increased the incidence of excitatory side effects.

Opiate premedication markedly reduced the incidence of these undesirable side effects.

A striking finding of this study was an increase in the incidence and severity of spontaneous abnormal muscle movements with dosage of B.137 and on occasions this convulsive activity could not be controlled without the use of a muscle relaxant.

Respiratory side effects were not a feature of B.137 anaesthesia.

Postoperative venous thrombosis and nausea and vomiting occurred more frequently with the methylated compound than with the other two thiobarbiturates.

The authors are of the opinion that B.137 can have no place in clinical anaesthesia.

ACKNOWLEDGMENTS

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RECOVERY TIME FROM METHOHEXITAL ANAESTHESIA

BY

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THERE is a need for an ultrashort acting barbiturate to give anaesthesia followed by a more rapid recovery than after thiopentone. In the outpatient and dental department the pleasant induction given only by an intravenous barbiturate must be combined with a rapid recovery from anaesthesia. Similarly, Caesarean section is an operation in which the patient receives no sedative premedication and it is desirable to induce anaesthesia by intravenous injection but the barbiturate must have a short action. It has been claimed that methohexital has a shorter action than thiopentone and on this assumption the drug at this time was in use in the dental department of the Royal Free Hospital. The impression was gained that the rate of recovery from methohexital and nitrous oxide and oxygen anaesthesia was indeed rapid with few side effects but objective evidence was needed to confirm this observation.

METHOD

The operation chosen for the clinical trial that was undertaken and is reported here, was evacuation of retained products of conception. The patients were all physically fit except for varying degrees of anaemia from blood loss. Some of the patients with septic abortions who were very ill or uraemic were excluded from the series. Alternate patients were anaesthetized using thiopentone, nitrous oxide and oxygen or methohexital, nitrous oxide and oxygen. There were 35 patients in each group.

Anaesthesia.

The author administered each anaesthetic personally. The premedication in each case consisted of papaveretum 20 mg and hyoscine 0.4 mg. Each patient was anaesthetized on the operating table. An approximate sleep dose of thiopentone 2½ per cent or methohexital 1 per cent was injected and was followed by more barbiturate, equivalent to half the sleep dose. Thus induction consisted of about one and a half times the sleep dose of the barbiturate. No airway was inserted and a mixture of 75 per cent nitrous oxide and oxygen was given at a flow rate of 8 litres per minute. The onset of anaesthesia was taken as the time at which the facepiece was applied. Additional doses of thiopentone or methohexital were given as required. The criteria for additional dosage were movement by the patient or swallowing and an effort was made to keep anaesthesia as light as possible. The time at which the facepiece was removed was taken as the end of anaesthesia. This took place almost immediately after the surgeon indicated that the operation was finished. An airway was then gently inserted, although some patients were too light to tolerate this stimulation. The patient was transferred directly from the table to the bed and placed in the lateral position. The patients were then left to recover quietly. The only stimulation occurred when the nurse counted the pulse. Spontaneous opening of the eyes was adopted as the criterion of recovery.

RESULTS

The recovery time in the thiopentone group varied from 4 to 102 minutes, the mean was 25.9 ± 3.7 and the standard deviation was 22.0.

The recovery time in the methohexital group varied from 2 to 30 minutes, the mean being 8.3 $\pm$ 1.01 and the standard duration was 6.0. The difference between these figures is statistically highly significant, $P<.001$ (fig. 1).

In the thiopentone group one patient would not tolerate an airway at the end of the anaesthetic. In the methohexital group 9 patients would not tolerate an airway at this time.

The lengths of the operations in the two groups did not vary widely. In the thiopentone group the durations ranged from 7 to 25 minutes with an

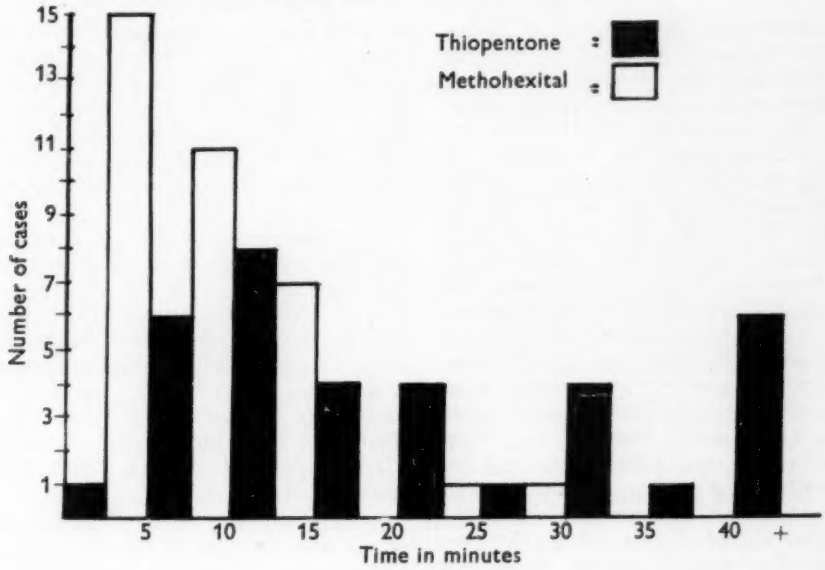

FIG. 1
Recovery time from methohexital anaesthesia.

average of 15 minutes. In the methohexital group the operations took from 7 to 33 minutes with an average of 14 minutes.

The dosage of barbiturate required in the two groups can be compared in table I which includes the findings reported by other workers.

TABLE I
Dosage of thiopentone and methohexital.

	Thiopentone		Methohexital	
	Max.	Min.	Max.	Min.
Jolly	725	250	260	100
Wyant and Chang	1000	250	510	140
Wyant and Barr	550	125	250	50

DISCUSSION

The principal difficulty in a comparison of this type is to eliminate the many variables that exist between patients, types of operation and the techniques of different anaesthetists. The only procedure needing anaesthesia that is repeated several times upon the same patient is modified electro-convulsive therapy but this investigation is mainly concerned with recovery from anaesthesia and it is possible that the effects of the electric current may affect recovery to some degree. The simple and relatively common operation of evacuation of retained products of conception was chosen for this trial as a certain amount of standardization was ensured. Firstly, all patients were females and all were within the age limits of child bearing. Secondly, the operation involves minor stimulation of a constant type as there is no need to dilate the cervix in the majority of cases. The author gave every anaesthetic in the series personally and no analysis of results was undertaken until all 70 anaesthetics had been given. An impression that recovery was more rapid from methohexital was unavoidable but whether this was significant or not was not known until the trial was completed.

A similar trial has been carried out by Wyant and Chang (1959) on patients undergoing minor gynaecological procedures. They used oxygen only as an inhalation agent. Methohexital was administered as a 1 per cent solution for induction and subsequently as an intravenous drip in 0.2

per cent concentration. This was a trial of methohexital rather than a specific test of recovery time but the more rapid recovery from methohexital was the most striking conclusion emerging from the series. The mean waking time from the last injection of thiopentone was 31 minutes 49 seconds and from the last injection of methohexital the mean waking time was 13 minutes 17 seconds. These times are similar to those observed in the present series but the time in the series of Wyant and Chang was measured from the last injection and not from the end of the operation. A second and similar trial carried out by Wyant and Barr (1960) was blind. Nitrous oxide and oxygen were used as inhalation agents and the barbiturates under test were administered by intermittent injection. Recovery times were much shorter than those found in the trial described by Wyant and Chang, and in the trial reported here and were measured from the end of the operation instead of from the last injection. The mean times were as follows: thiopentone anaesthesia 7.7 minutes; methohexital anaesthesia 2.7 minutes. The difference between these means is still highly significant.

The criterion of recovery is important. All that is required of anaesthesia for inpatients is that the patient should recover his cough reflex, reject his airway and perhaps open his eyes and speak. He will probably lapse into sleep again if he is not in pain.

Some of the variation in recovery time in short operations, such as dilatation and curettage, is due to the varying effect of the premedication. In the work of Wyant and Chang, and Wyant and Barr the end point of recovery was taken to be the time at which the patient responded to a command. In the present investigation the patients were left until they opened their eyes spontaneously. This may well account for the longer recovery time reported here. The degree of recovery adequate in inpatients is obviously not sufficient for outpatient anaesthesia where lucid thought, normal reaction time and an absence of symptoms such as dizziness, nausea or headache are required. The comparison with thiopentone as a standard shows the shorter recovery time from methohexital anaesthesia with remarkable clearness. A trial by Green and Jolly (1960) has been carried out on dental outpatients and showed that good recovery occurred in ambulant patients following anaesthesia in the dental chair.

Despite the fact that the trial reported in this paper was primarily to measure the recovery time from anaesthesia, several other characteristics of methohexital anaesthesia were noted and are of interest when compared with the comments of other writers.

A comparison of the potency of methohexital with that of thiopentone has been carried out by the author using modified electro-convulsive therapy anaesthesia and prior to the use of the drug in the dental department. This will be reported. The ratio of thiopentone dosage to that of methohexital was 1:3.1. The ratio of the average doses found in this series was 1:2.4. Wyant and Barr (1960) found the ratio to be 1:2.5. Taylor and Stoelting (1960) found the ratio to be about 1:3.

Apnoea following methohexital has been reported but was scarcely noticed in this series. Following the injection of a sleep dose a short time elapsed while the facepiece was applied and the anaesthetic gases were turned on. This took a few seconds during which the patient may have been apnoeic but spontaneous respiration began as soon as the facepiece was adjusted. Assisted respiration was needed only a few times and for a few breaths. Cyanosis never occurred. This has been confirmed by experience of methohexital in dentistry when assisted respiration was not required in 500 patients. Two other symptoms which have been recorded are hiccough (Taylor and Stoelting, 1960; Wyant and Chang, 1959) and muscular twitchings (Taylor and Stoelting, 1960). In this series hiccough was not seen with thiopentone or methohexital. Muscular twitchings were not noticed and this symptom was not remarked upon by Wyant and his colleagues. A disturbing symptom reported by Taylor and Stoelting (1960) was pain at the site of the injection or along the vein. This was said to occur in 60 per cent of patients but it has never been seen by the author and was not mentioned by Wyant and his colleagues. Anaesthesia with methohexital was similar to anaesthesia with thiopentone except for the more rapid recovery after the former. The impression was gained that maintenance with methohexital was less smooth than with thiopentone.

SUMMARY

Thirty-five patients were anaesthetized using thiopentone, nitrous oxide and oxygen. Thirty-five comparable patients were anaesthetized using methohexital, nitrous oxide and oxygen. The operation performed in each case was for the evacuation of retained products of conception. The recovery time from each anaesthetic was measured. The recovery from methohexital anaesthesia was found to be significantly shorter than recovery from thiopentone anaesthesia.

The findings are discussed and compared with those in other papers on methohexital.

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THE INFLUENCE OF CHLORPROMAZINE AND HYDERGINE ON PETHIDINE AND SCOPOLAMINE PREMEDICATION

BY

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IN an endeavour to potentiate the effect of pethidine and scopolamine premedication, the drugs chlorpromazine and hydergine were investigated, particularly in regard to their effects on the autonomic nervous system.

A comparison was made between three comparable series of patients. One series acted as a control and the other series had chlorpromazine and hydergine respectively. Changes in pulse rate and blood pressure, the presence of sweating and a clinical assessment of the effectiveness of the premedication were employed to estimate the value of the addition of the two drugs.

MATERIAL AND METHODS

Each series comprised 50 unselected cases. The sex and age distribution were similar in each series (see table I). Standardized doses of pethidine and scopolamine (pethidine 10 mg and scopolamine 0.04 mg (1/1500 grain) per stone (6.3 kg) body weight) were given, and the dose of chlorpromazine was 5 mg/stone body weight and for hydergine 0.3 mg/stone body weight. The dose for hydergine is higher than that normally employed because a preliminary pilot trial indicated that smaller doses produced no significant effects. For patients of 65 years of age and over these doses were halved following usual practice. The premedication was given intramuscularly 1 to 1½ hours before induction of anaesthesia and its effect assessed just prior to induction.

RESULTS

The results obtained in all the tests are summarized in table I.

Premedication was deemed unsatisfactory when the patient appeared apprehensive or complained of some discomfort. Among the group considered unsatisfactory are those cases where vomiting actually occurred.

The next column in the table records the cases where sweating occurred.

Pulse rate changes are recorded as positive when the increase was 15 beats or more per minute, and negative when the decrease was 15 beats or more per minute. This criterion was adopted in order to eliminate small changes in pulse rate which may well have been irrelevant.

Similarly, blood pressure changes have only

TABLE I

Drugs	Sex		Age range in years	No. of cases						
	M.	F.		Premedication unsatisfactory	Vomiting	Sweating	P.R.		B.P.	
							+	−	+	−
Pethidine and scopolamine alone	29	21	28–79	8	0	16	13	3	5	14
Pethidine, scopolamine and chlorpromazine	22	28	24–77	2	0	4	20	3	1	41
Pethidine, scopolamine and hydergine	24	26	26–77	15	7	17	3	11	1	35

been recorded when the change was 20 mm Hg or more, plus indicating an increase and minus a decrease of this magnitude.

DISCUSSION

The number of cases where premedication was unsatisfactory is only significantly different for the two series where chlorpromazine and hydergine were used. Here chlorpromazine was significantly better than hydergine at the 1 per cent level ($\chi^2 = 10.21$) and this was borne out by the incidence of vomiting with hydergine.

Sweating occurred less frequently when chlorpromazine was used ($\chi^2 = 7.56$ for a comparison between this series and that for pethidine and scopolamine alone; significant at the 1 per cent level).

The effects of the drugs on pulse rate and blood pressure were examined by scoring one for an increase, minus one for a decrease, and zero for no appreciable change, and applying t tests with 98 degrees of freedom to the differences between mean scores.

The addition of chlorpromazine did not produce a significant alteration in the pulse rate changes but hydergine produced a change significant at the 1 per cent level ($t = 3.45$). The effect is a tendency to a reduction in pulse rate.

These results appear to support the conclusion of Ngai and Wang (1955) that hydergine has a somewhat stronger adrenergic blocking action than chlorpromazine.

Both drugs cause a highly significant reduction in blood pressure compared to pethidine and scopolamine alone ($t = 5.86$ for chlorpromazine and 4.50 for hydergine) but there is no significant difference between their effects.

CONCLUSIONS

Both chlorpromazine and hydergine produced a significant reduction in blood pressure.

Chlorpromazine produced a significant reduction in the incidence of sweating but did not produce a significant effect on the pulse rate.

Hydergine produced a significant reduction in pulse rate but increased substantially the incidence of unsatisfactory premedication, especially nausea and vomiting.

ACKNOWLEDGMENTS

Our thanks are due to Messrs. Sandoz Products, Ltd., for a liberal supply of special 2 ml ampoules containing 1 mg Hydergine per ml and to Mr. W. Brass, Department of Statistics, University of Aberdeen, for statistical help.

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ANTIHISTAMINE DRUGS IN PRE-ANAESTHETIC MEDICATION: BLIND STUDIES ON 953 PATIENTS

BY

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THE side effects of drowsiness associated with antihistamine therapy aroused our interest in the potential usefulness of these drugs for pre-operative sedation. It was felt on superficial clinical observation that the circulatory and respiratory depressive effects as compared to those attendant upon the narcotic analgesics and barbiturates were relatively absent.

Loew (1946) synthesized a series of benzhydryl ethers from which diphenhydramine emerged as an antihistamine of considerable potential. The sedative action of this compound is related to the ether linkage in the molecule as compared to the nitrogen bridge in other antihistamines such as tripelennamine. The sedative action of diphenhydramine was studied in the obstetrical patient and subsequently reported by Cappe and Pallin (1954). More recently, Lear (1958) reported on comparative studies in which diphenhydramine was used as an adjunct to pre-anaesthetic medication.

In the mid-1940's, French scientists working independently of the Americans, synthesized a number of derivatives of phenothiazine in search for useful antihistamine drugs. Of these compounds, promethazine appeared most promising in view of its potent antihistamine action and minimal toxicity. Drowsiness was quite marked with promethazine so that Halpern (1949) suggested the concomitant use of amphetamine. The sedative use of promethazine in anaesthesia was employed by the French in the late 1940's.

Subsequent compounds derived from phenothiazine gained prominence as tranquillizers and anti-emetic drugs. Within the past two years another phenothiazine of significant antihistamine potential was synthesized, its generic name being trimeprazine.* This compound has been shown to be more potent than promethazine in combating histamine-induced bronchospasm in the experimental animal. Our preliminary study has also indicated that useful sedative properties are present in trimeprazine.

Another antihistamine of potential use in pre-anaesthetic medication is the diphenylmethane, hydroxyzine. This compound appears to be a chemical hybrid of the antihistamines diphenhydramine and chlorcyclizine (see figure 1). Farah (1956) reported on the use of hydroxyzine as an ataractic. More recently the antihistamine activity of this compound has been appreciated.

PURPOSE AND TECHNIQUE OF STUDY

Many comments have appeared with regard to the overall usefulness of the newer antihistamine drugs as adjuncts to the anaesthetic management of the presurgical patient; there has resulted a great deal of contradiction with subsequent confusion. It was decided, therefore, to screen three of the major antihistamine drugs utilizing blind techniques in an attempt to determine their relative effectiveness as adjuncts to pre-anaesthetic medication. The study technique was based on the ability of commonly used drug doses to enhance pre-operative sedation when combined with a standard narcotic such as pethidine. The dose range of narcotic analgesic was deliberately halved in order to minimize narcotic-induced side effects.

Since the drug action under investigation was not a primary function of these compounds, it was necessary to base the dose schedule on our

* Trimeprazine is marketed as Vallergan in Great Britain.

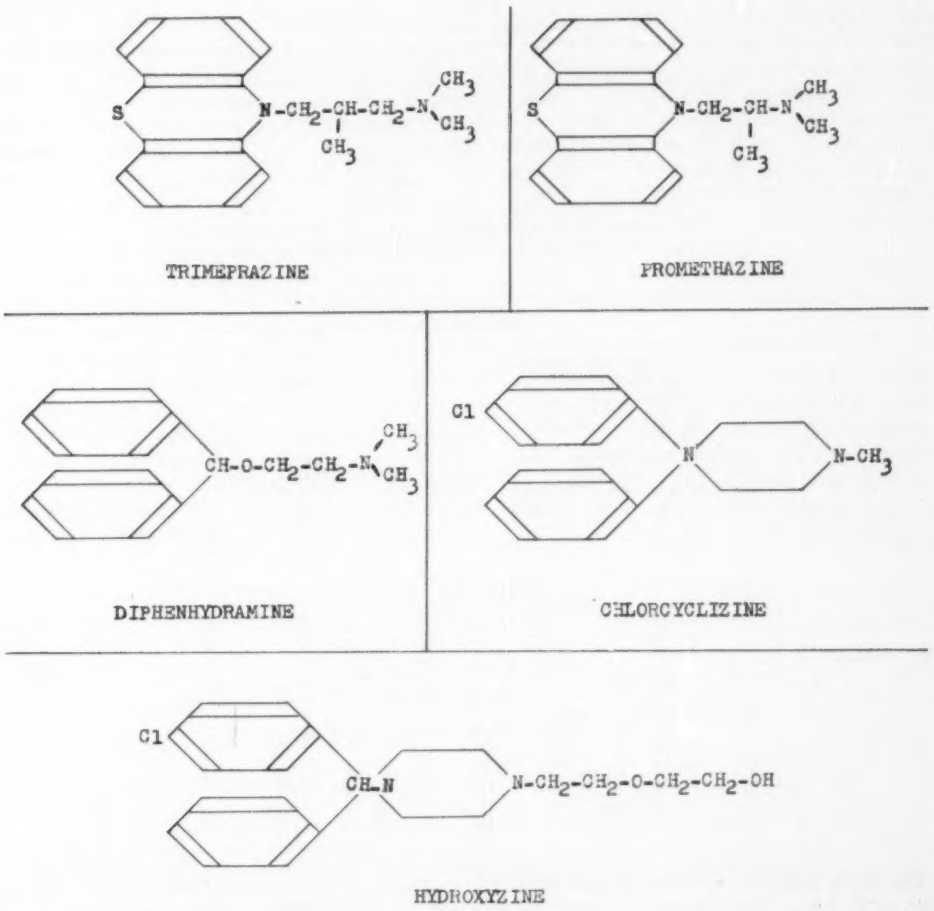

FIG. 1

previous experiences with these compounds as "pilot material", and on common usage by other investigators. The premedicating schedule was arranged to permit the unknown material to be administered in millimetres of solution or fractions thereof, according to the age and physical status of the patients. Only one dose of test drug was given to each patient. The drug was administered intramuscularly 2 hours pre-operatively.

The present report is based on data obtained from blind studies conducted with promethazine, trimeprazine and hydroxyzine. Previous studies had determined that diphenhydramine was less satisfactory than promethazine in premedication.

The preponderance of the data in this report was obtained from the patient population of a large municipal hospital. The case distribution was similar within each drug series. Premedication was supervised by the research fellow who was not aware of the drugs under investigation. The premedicating schedule is shown in table I. Dose distribution according to age is shown in table II. Data were recorded on specially designed check-off sheets. The work sheets were checked daily and only those satisfactorily completed were used for the tabulation of these data.

TABLE I
*Pre-anaesthetic medication schedule.**

Age groups (years)	2 hours pre-op. antihistamine (I.M.) (mg)	1 hour pre-op. narcotic (I.M.) (mg)	1 hour pre-op. atropine (I.M.) (mg)
12–40	50	50	0.4–0.3
41–55	50–35	50–35	0.3
56–70	35–25	35–25	0.3–0.2
71 and over	25–12.5	25–12.5	0.2

* Antihistamine drugs were actually ordered in terms of millilitres of an unknown solution. Each patient received one intramuscular dose only.

TABLE II
Dose distribution.

A. Trimeprazine (215 cases)						
Age group	50 mg		35 mg	25 mg	12.5 mg	
16–40	63		2	0	0	
41–55	36		4	1	0	
56–70	12		22	10	3	
71 and over	1		0	18	43	
B. Promethazine (271 cases)						
16–40	70		10	0	0	
41–55	63		5	2	0	
56–70	8		21	26	0	
71 and over	0		2	26	38	
C. Hydroxyzine (262 cases)						
16–40	88		7	2	0	
41–55	27		3	0	0	
56–70	10		30	35	0	
71 and over	0		2	10	48	
D. Pethidine (151 cases)						
Age group	100 mg	75 mg	50 mg	35 mg	25 mg	12.5 mg
12–40	18	13	7	1	0	0
41–55	21	7	3	0	0	0
56–70	13	13	15	2	2	2
71 and over	0	5	7	6	14	2

The study population ranged in age from 12 years to 95 years. Observations were made on the pre-operative sedation, the stability of blood pressure in the pre- and postoperative period, the incidence and severity of postoperative nausea and vomiting, and finally the postoperative narcotic requirement. The data were based on the effects created by the single pre-operative administration of drug. The surgery encountered included all types of major intra-abdominal surgery, head and neck, orthopaedic, and radical breast surgery. Miscellaneous procedures also included hernia repair, cystoscopic and transurethral procedures, vaginal plastic, and rectal surgery. The anaesthetic techniques utilized in the study are shown in table III.

TABLE III
Anaesthetic techniques (total series).

	Total cases	% of study
A. General anaesthesia		
Cyclopropane	397	42
Nitrous oxide	230	24
B. Conduction anaesthesia		
Spinal	278	29
Epidural/Caudal	19	2
Nerve block	10	1
Local	19	2

Ratio of general anaesthesia to conduction anaesthesia was similar in each drug group. Approximately 25 per cent of each study group underwent intra-abdominal surgery. 75 per cent underwent extra-abdominal procedures.

PRE-OPERATIVE SEDATION

The psychic state of each patient was evaluated and classified as calm, apprehensive, or disoriented. Each of these classifications was subdivided further on the basis of whether the patients were awake, drowsy, or asleep. All patients classified as calm (awake, drowsy, or asleep) were considered as being adequately sedated. A source of possible error in this scheme of tabulation is the fact that the dividing line between the awake-calm and the awake-apprehensive patient is often difficult to ascertain. The "sedation-index" was devised, therefore, as a supplemental aid in the evaluation of the drug effect of the various premedicants. The "sedation-index" is the ratio of the percentage of the "drowsy and asleep" patients to the overall percentage of adequately sedated patients in the "calm" classification. The statistics for pre-operative sedative sedation with antihistamine-supplemented premedication and with standard premedication are shown in table IV.

The "sedation-index" for pethidine is based on a control series of 151 patients of the same hospital population and with similar case distribution to the remainder of the study. The "sedation-index" used in conjunction with the percentage of overall sedation, provides the basis for a better method of evaluating pre-operative sedation within our parameters. The error caused by inclusion of an awake-apprehensive patient in the awake-calm classification is reduced. In this manner the subjective error in the evaluation of the pre-operative patient is minimized.

BLOOD PRESSURE EFECT

An area of major concern with all premedicating agents is their effect on the vascular stability of the patient as reflected in the blood pressure readings. Data were obtained in this study to ascertain whether blood pressures were altered significantly by a single dose of antihistamine plus a half-dose of pethidine, all administered intramuscularly. Significant hypotension was considered to be any drop of 40 mm Hg or greater. This particular figure represented a fall in pressure between 25 per cent and 33 per cent of the patients' control levels. The incidence of significant pre-operative hypotension in the control series (no antihistamine but pethidine full dose) was found to be 9.5 per cent; the antihistamine series with pethidine (half-doses) was associated with an 11 per cent occurrence of significant hypotension. Thus the pre-operative

TABLE IV
Pre-operative sedation.

Patients	Drug	Calm awake		Calm drowsy		Calm asleep		Adequately sedated	
		%	No. pts.	%	No. pts.	%	No. pts.	%	No. pts.
215	Trimeprazine	41.0	88	33.5	72	2.5	5	77.0	165
271	Promethazine	50.0	135	13.5	37	2.0	5	65.5	177
262	Hydroxyzine	54.0	141	9.5	25	0	0	63.5	166
151	Pethidine	53.5	81	9.0	13	2.5	4	65.0	98

Chi-square test applied to all four drugs indicates one different drug response ($P<0.01$). Trimeprazine *v.* other three drugs pooled ($P<0.001$) indicates that trimeprazine is significantly different.

*Sedation index.**

Trimeprazine	4.7	Pethidine	1.8
Promethazine	2.4	Hydroxyzine	1.5

* Ratio of calm (drowsy and asleep) to total adequately sedated.

Statistical analysis of these results using the "chi-square" test reveals the following information based on the adequately sedated column. A comparison of the four drugs indicates at least one different drug response ($P<0.01$). Trimeprazine was next compared to the other three drugs (pooled) with the result indicating that this was the different drug ($P<0.001$). The chi-square values for the preceding analysis were 11.456 and 11.197 indicating no statistically significant differences among the other drugs.

patients receiving antihistamine-supplemented premedication exhibited a negligible increase in the incidence of pre-operative hypotension when compared to standard medication.

Blood pressures during anaesthesia were not adversely affected by the pre-operative use of antihistamine medication.

The continuance of pre-operative drug effect into the immediate postoperative period was studied with regard to the blood pressure. The same criterion was applied in the postoperative patient; that is, pressure falls of 40 mm Hg or more as compared to the unmedicated control for the individual patient. Those patients in whom postoperative bleeding occurred in the recovery room were excluded from this portion of the study. The overall incidence of significant hypotension has been shown in table V. The mean duration of hypotension for the various premedicant drugs has been included, as well as data on chlorpromazine-supplemented premedication for the purposes of comparison. In all series it was noted that hypotension occurred twice as frequently in the patients above 56 years of age as compared to those below this age figure.

TABLE V

*Postoperative hypotension.**

Drug	% incidence of hypotension	Mean duration (minutes)
Trimeprazine	18.0	100
Pethidine	18.0	150
Promethazine	13.5	160
Hydroxyzine	16.5	165
Chlorpromazine†	34.0	240

* The result of premedication and anaesthesia (haemorrhage or shock excluded). No additional antihistamine given other than single pre-operative dose (I.M.).

† Inserted for purposes of comparison.

RECOVERY ROOM PHASE

In addition to the blood pressure observations in the recovery room patients, the incidence and severity of nausea and vomiting was studied. The control series (pethidine) showed an incidence of 25 per cent for this complication. The series in which antihistamines were used to supplement premedication showed lower incidences as follows: trimeprazine 8 per cent; hydroxyzine 9.5 per cent; promethazine 9.5 per cent. The chi-square test comparing pethidine against all the other drugs yields $P<0.001$, suggesting a significant difference. There was no significant difference, however, in the incidence of sickness in the groups given antihistamine drugs.

The study groups were further analyzed with regard to the sex distribution, the type of anaesthesia, the surgical procedure. The ratio of male to female patients was found to be nearly 1:1 in all the groups. Nausea and vomiting occurred in the female patients with greater frequency than the males (4:1). The comparative data with regard to type of anaesthesia and surgical procedure are shown in table VI. Since the number of cases within a particular sub-group was found to be small it was only possible to group procedures according to whether they involved intra-abdominal surgery or extra-abdominal surgery.

The narcotic requirements were tabulated for the postoperative patients during their first 3 hours in the recovery room. The first 3 hours seemed sufficient time for the majority of the patients requesting pain relief do so within this time period. The control series which had received

TABLE VI

Percentage of postoperative nausea and vomiting (recovery room).

	Trimeprazine	Hydroxyzine	Promethazine	Pethidine
Type of anaesthesia				
General	15	20	21	34
Conduction	3	5	5	4
Surgical procedure				
Intra-abdominal	13	15	13	18
Extra-abdominal	5	10	13	20

The sex distribution within each series was approximately 1 : 1. Nausea and vomiting occurred four times as frequently in females as compared with males, regardless of surgical procedure or type of anaesthesia employed.

standard premedication required pain-relieving narcotics in 27 per cent of the group within the first 3 hours. Trimeprazine premedication was associated with an 18 per cent incidence of narcotic requirement; promethazine and hydroxyzine appeared no better than standard premedication (30 per cent).

DISCUSSION

Anaesthetic premedication has remained relatively unchanged since Labbé and Guyon introduced morphine to clinical anaesthesia in 1872. The addition of scopolamine to enhance preoperative amnesia and depress secretory activity, became common some thirty years later. Pethidine was substituted for pre-operative morphine in many centres following its synthesis in 1937. As newer anaesthetic agents such as cyclopropane were introduced, the need for heavy narcotic premedication was challenged. The odour of cyclopropane was not unpleasant as had been the case with ether, nor were inductions prolonged when cyclopropane was administered. Patients receiving full doses of pre-operative narcotic often became apnoeic during induction of anaesthesia with cyclopropane and literally prevented themselves from becoming anaesthetized in the absence of ventilatory assistance from the anaesthetist. Perhaps for reasons such as these some investigators insisted that pre-operative medication should consist of a barbiturate combined with a belladonna derivative in the pain-free patient. Under specific circumstances this type of premedication may appear justified where the patient desires and eagerly anticipates surgery in contrast to the patient who views surgery with considerable trepidation, or may even be terrified by the prospect. The frightened patient will not be calmed by a token dose of pentobarbitone. These patients frequently beg to be asleep before they leave their room for the operating theatre.

The problem of providing psychic sedation for the patient going to the operating theatre obviously must be resolved by finding a middle road between the various philosophies of pre-anaesthetic medication. The possibility of using halved doses of pre-operative narcotic and thus reducing undesirable side effects was tried some years ago in our department. Placebo material was given 2 hours prior to surgery and was followed by half-doses of pethidine and belladonna (atropine) 1 hour preoperatively. The placebo material was added simply to mislead the observers with respect to the actual purpose of the study. Sedation was found to be barely adequate when half-doses of pethidine were supplemented with placebo material.

The synthesis of the phenothiazine derivatives with their specific actions on the subcortical centres concerned with the production of stress and emotion seemed to be the long awaited breakthrough in premedication. Severe forms of hypotension were encountered with the earlier compounds of this series and so their use was considered to be fraught with danger. Amongst this series of compounds was the antihistamine drug promethazine which was found to disturb blood pressure minimally. When used alone, promethazine was not a dependable sedative but when combined with reduced doses of pethidine, adequate pre-operative sedation could be accomplished. More recently another antihistamine of the phenothiazine series was synthesized. The compound, trimeprazine, was found to produce a useful degree of sedation in addition to its antihistamine properties. About the same time the ataractic-antihistamine, hydroxyzine, was introduced. In a continuing search for compounds of potential use in anaesthesia, the three antihistamine drugs mentioned above were screened using blind study techniques. These drugs were combined in pre-operative medication with halved doses of pethidine and the results studied.

The most difficult and least objective part of the study was the evaluation of the effectiveness of sedation afforded by antihistamine-supplemented pre-anaesthetic medication. Our system of classification by means of the psychic state of the patient was designed to make this task as objective as possible. A "sedation-index" was suggested in order to describe more accurately the relative effectiveness of the drugs. The "sedation-index" parallels the actual sedation produced by the pre-operative drugs. The higher "sedation-index" is associated with better pre-operative sedation. While the overall incidence of adequate sedation was similar for promethazine and hydroxyzine, comparison of the "sedation-index" for these two drugs indicates that promethazine is more effective as a premedicant than hydroxy-

zine. Trimeprazine produced a higher incidence of adequate sedation than either of the other drugs tested; the "sedation-index" parallels this finding. While the overall incidence of adequate sedation is similar for trimeprazine and chlorpromazine, trimeprazine has a "sedation-index" of 4.7 as compared to 3.6 for chlorpromazine; trimeprazine was noted to be a more effective pre-operative sedative than chlorpromazine. The control series which had received full doses of pethidine pre-operatively had a "sedation-index" of 1.8 suggesting that standard premedication is not as effective as supplemented pre-anaesthetic medication. In this regard only hydroxyzine was less effective than the other antihistamines tested.

Examination of the data on blood pressure disturbance revealed that the three test drugs compared favourably with standard doses of pethidine as regards the incidence and duration of significant hypotension. In evaluating these data each series was screened to be certain that the distribution of the elderly patients was similar throughout the study. This was deemed necessary because of the increased incidence of hypotension in the elderly patients. The number of patients with admission pressures greater than 140/90 mm Hg was also ascertained for each series, since significant hypotension was noted to occur more frequently in these patients. The distribution of hypertensive patients was similar throughout all the study groups.

Numerous reports over the years have implied that phenothiazine premedication was associated with a reduction in undesirable reflex activity during anaesthesia and a smoother anaesthetic course generally. It has not been possible to devise any method for confirming these statements during these studies. The anaesthetists connected with the study were unable to detect any significant differences amongst the various premedicants as regards their effect on the course of anaesthesia.

There was no evidence of local toxicity other than the complaint of pain of a short duration following the injection of antihistamine. This complaint was more frequent in female patients, yet the overall incidence of this complaint was small. There was also no evidence of generalized toxicity in the dose ranges we employed with the test drugs. Extrapyramidal manifestations have been encountered during studies with related compounds administered according to the techniques herein described.

One of the advantages of antihistamine-supplemented premedication is the reduction in the incidence and severity of postoperative complications such as retching, nausea, and vomiting. While many factors influence postoperative nausea and vomiting, either favourably or unfavourably, there is a general reduction in this complication in the overall recovery room population when premedicated with one of the three study drugs. Regardless of the possible central mechanisms of anti-emetic activity with the antihistamines, the less abrupt emergence from anaesthesia associated with the use of these drugs in premedication is responsible to a significant degree for the reduction in postoperative nausea and vomiting. The incidence was similar for the three study drugs; and was one-third of the incidence observed after the use of standard premedication.

A significant reduction in the postoperative narcotic requirements was noted in those patients who received trimeprazine in their premedication. Promethazine and hydroxyzine were found to be less effective in this regard.

SUMMARY

Three antihistamine drugs were studied as adjuncts to pre-anaesthetic medication: trimeprazine, promethazine, and hydroxyzine. The investigations were carried out utilizing blind techniques and control patients.

Adequate sedation was obtained despite a reduction in pre-operative narcotic. Significant hypotension was not a problem with this type of premedication. There was a reduction in postoperative nausea and vomiting and in the narcotic requirement in the antihistamine groups as compared with control patients.

The antihistamine, trimeprazine, produced excellent pre-operative sedation. Postoperative hypotension with this drug was of a shorter duration than in those patients who had received standard premedication.

Drug toxicity was not a problem with the antihistamines studied.

ACKNOWLEDGMENTS

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Promethazine (Phenergan[R]) was supplied through the courtesy of Mr. George Alpern of Wyeth Laboratories Philadelphia.

Hydroxyzine (Vistaril[R], Atarax[R]) was supplied through the courtesy of Mr. Jack Spencer of Chas. Pfizer Co., Brooklyn.

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CLINICAL TRIAL OF WIN 14,098: A NEW ANALGESIC AGENT

BY

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PETHIDINE was the first potent synthetic analgesic agent. Numerous other compounds have since been prepared, one of the more recent being WIN 14,098 (ethyl 4-phenyl-1-[3-(phenylamino)propyl] piperidine-4-carboxylate ethanesulphonate).

Structurally similar to pethidine (fig. 1), WIN 14,098 was synthesized by Elpern (1954).

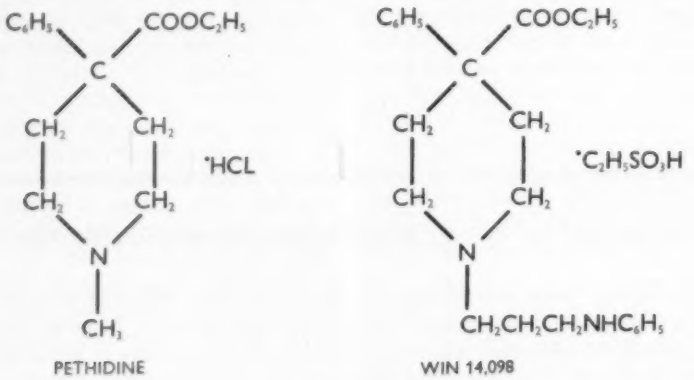

FIG. 1
Structural formulae of pethidine and WIN 14,098.

In rats and monkeys WIN 14,098 was found to be a more potent analgesic than pethidine, yet causing less respiratory depression.

Clinical trials have been carried out at the Sterling-Winthrop Research Institute and reports of other clinical studies have been published in the American literature by DeKornfeld and Lasagna (1959), Groeber and Ziserman (1959) and Sadove et al. (1960). These reports concern only the oral or intramuscular administration of the drug and confirm its potent analgesic activity.

New synthetic analgesic drugs are made available and tested in the hope that they may possess the following properties: potent analgesic action; minimal sedative effect; minimal effect on respiration; absence of other side effects.

The present investigation was performed in order to make a preliminary evaluation of WIN 14,098 in relation to these properties. The limitations of this study are appreciated, since no comparison between WIN 14,098 and other drugs is reported, and further work is being undertaken to establish its potency in relation to morphia.

METHOD

Three groups of patients were used. The first consisted of 100 patients with postoperative pain severe enough to indicate the use of a potent analgesic. These patients were given a standard dose of WIN 14,098 (20 mg) by intramuscular injection. One hour later they were asked: "How is your pain?" and were offered a choice of the following five assessments: "gone", "much better", "better", "same", "worse". They were then asked: "Did

you notice any other effects of the injection?" Leading questions were not asked. The injections were given by the nursing staff who were invited to comment on the action of the drug.

WIN 14,098 was given only to patients who had fully recovered from anaesthesia and it was not given within 4 hours of any other analgesic or sedative agent. There were 55 males and 45 females in this group and their average age was 49.7 years. The youngest patient was aged 14 years and the oldest 81 years. All had undergone major surgery, the operative procedures being listed in table I.

TABLE I

Operative procedure	No. of patients
Thoracotomy	45*
Upper abdominal operations	9
Lower abdominal operations	11
Herniorrhaphy	4
Mastectomy	8
Orthopaedic operations	17
Miscellaneous	9
Total	103†

*Including 28 pulmonary resections.
†Three patients underwent double procedures.

In the second group 20 healthy young adults received an intramuscular injection of WIN 14,098 (20 mg), together with atropine 0.6 mg as premedication 1 hour prior to anaesthesia for minor surgical procedures. The degree of sedation was observed.

A third group of 7 fit women aged between 22 and 45 years and weighing between 92 and 145 lb. (41.4–65.2 kg) received atropine 0.6 mg only, prior to anaesthesia for minor gynaecological surgery. Anaesthesia was induced with a small dose of thiopentone (300–425 mg) and was maintained with nitrous oxide and oxygen (6 l./min and 2 l./min) and halothane 0.9 per cent. When anaesthesia had been stabilized an intravenous injection of WIN 14,098 0.05 mg/lb. (0.45 kg) as a 0.1 per cent solution was given. The effect on respiration was observed. Other apparent effects were also noted.

RESULTS

WIN 14,098 for relief of postoperative pain.

Figure 2 summarizes the results in this group of patients. WIN 14,098 appeared to be a potent and generally reliable analgesic agent.

In reply to the question: "Did you notice any other effect of the injection?" 78 of the 100 patients said they had not.

Sleepiness was reported in 21 cases, nausea in 2, sweating in 2 and dryness of the mouth in 2. (Various other symptoms, each encountered in one case only, were not apparently significant.)

The nursing staff reported 3 cases of oversedation, 2 of sweating and 2 of nausea and vomiting apparently associated with the injection of WIN 14,098. The combination of absence of drowsiness with satisfactory analgesia was remarked in 13 cases.

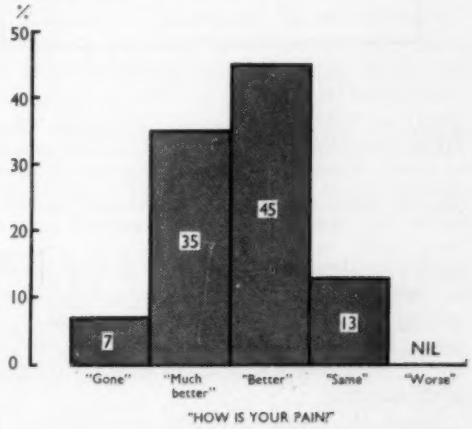

FIG. 2

Effect of WIN 14,098 20 mg on postoperative pain in a series of 100 cases.

None of the cases gave rise to concern and there was no instance of local reaction to the injection.

Premedication with WIN 14,098.

Of the 20 patients none appeared at all drowsy. On being asked: "Do you feel sleepy?" 8 said they did not and 12 indicated slight subjective sedation. Induction of anaesthesia appeared smoother than is usual when premedication consists of atropine alone. Induction of anaesthesia with thiopentone produced no more than the usual degree of respiratory depression.

Intravenous WIN 14,098.

Figure 3 shows the respiratory rates of the 7 patients before the intravenous injection of WIN 14,098 and afterwards at the time of maximum

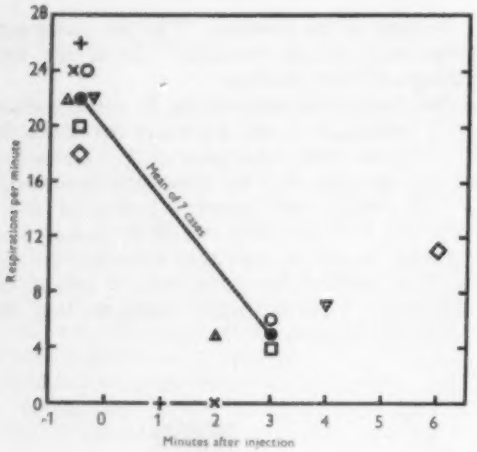

FIG. 3

Respiratory depression following intravenous WIN 14,098 0.05 mg/lb. Each of the 7 patients is represented by a pair of similar symbols. In each case the post-injection symbol indicates the respiratory rate at the time of maximum respiratory depression and also shows when this occurred.

respiratory depression. The mean of these results is indicated. The respiratory rate fell by an average of 77 per cent. Apnoea occurred in 2 cases. Respiratory depression appeared rapidly and in 5 patients was maximal within 3 minutes of the injection.

About 10 minutes after the administration of WIN 14,098, and after maximum respiratory depression had been observed, nalorphine was given with good effect in all cases. A nalorphine: WIN 14,098 ratio of 2:1 (w/w) was found to be appropriate.

No significant effect on pulse rate was observed. In 3 patients the rate increased by up to 9 per cent and in 4 it fell by up to 10 per cent. The mean result was a fall of 4 per cent. Blood pressure changes were minimal. The greatest rise was from 110/75 mm Hg to 130/80 mm Hg and the greatest fall from 100/70 mm Hg to 90/60 mm Hg.

No other general or local effects were observed. Clinically, recovery of consciousness appeared to be delayed and there was an average interval of 19 minutes between the end of anaesthesia and the time at which sensible answers could be given to simple questions. (Note that, as stated, these patients had received nalorphine.)

DISCUSSION

The response of those patients given WIN 14,098 for the relief of pain confirms that this agent is a powerful analgesic. Clinical observation indicates that a 20-mg dose of WIN 14,098 is about as potent as pethidine 100 mg. The age and physical condition of these patients varied greatly and they had undergone a variety of surgical procedures. In no case did the response to the standard 20-mg dose of the drug cause concern and this indicates that WIN 14,098 is a safe agent. The hypnotic effect is not marked and other side effects are minimal. In particular nausea and vomiting are not provoked. Considerable respiratory depression followed the intravenous administration of the drug, however, and care is necessary when it is given by this route.

WIN 14,098 appears to be worthy of further clinical trial and a more critical study of the analgesic properties and side effects of the drug, in comparison with morphine and a placebo, is being undertaken.

SUMMARY

One hundred patients received WIN 14,098 in 20-mg doses intramuscularly for relief of post-operative pain, 20 patients were given the same dose prior to anaesthesia, and a further 7 received an intravenous injection of 0.05 mg/lb.

WIN 14,098 produced good analgesia. Side effects were minimal in the first two groups of patients, but, in the third, marked respiratory depression occurred.

Further trial of this drug is suggested but care is recommended when it is given intravenously.

ACKNOWLEDGMENTS

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METHOHEXITAL IN DENTAL ANAESTHESIA

BY

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IN the majority of anaesthetics given to patients in the dental surgery or clinic the agents used are nitrous oxide and oxygen with or without a supplement such as trichloroethylene. If nitrous oxide with oxygen or air is used alone then it is often difficult to obtain satisfactory conditions for the dentist without subjecting the patient to some degree of hypoxia. There is no doubt that hypoxia is harmful even if the effects are not always immediately apparent (Bedford, 1955). Tom (1956) and Mostert (1958) in this country have separately described a technique whereby nitrous oxide and oxygen can be administered without hypoxia but giving adequate analgesia and a quiescent patient, although they admit that induction may be rather prolonged. Mushin (1952) estimates that from 7 to 10 minutes is required to achieve saturation with nitrous oxide using 80 per cent nitrous oxide and 20 per cent oxygen. In addition in the so-called "resistant" patient satisfactory conditions sometimes cannot be achieved and even the addition of trichloroethylene does not always give good anaesthesia. Thiopentone is sometimes used for induction in these patients but the recovery period is often prolonged and, in the light of our present knowledge, the patient needs escorting home.

Bourne (1952) condemned the illogical use of weak anaesthetic agents in out-patient anaesthesia and stressed the need for a "powerful" anaesthetic which is rapidly excreted. He has described the use of cyclopropane and oxygen for dental anaesthesia and has devised a piece of apparatus which enables a rapid induction and eliminates the risk of explosion. However, there is a high incidence of nausea and vomiting afterwards; in one series Bourne states that 21 per cent of patients vomited and 12 per cent were nauseated. The risk of explosion, unless special apparatus is used, and the high nausea and vomiting rate rather invalidate this otherwise suitable agent.

Induction of anaesthesia by an intravenous injection is preferred by the majority of patients to induction by inhalation of gas or vapour and if this can be combined with tranquil maintenance and a rapid recovery free from nausea and vomiting, then an approach will have been made toward an ideal dental anaesthetic technique.

Preliminary use of methohexital suggested that it is an ultrashort-acting barbiturate from which recovery is more rapid than after thiopentone. Encouraged by this a clinical trial was carried out in the Dental Out-patient Department of the Royal Free Hospital. The structural formula is shown in figure 1. The molecule contains two asymmetric carbon atoms so that two d- l- pairs exist capable of resolution into optically active d and l forms. Methohexital is the racemic form.

PRELIMINARY INVESTIGATIONS

Before the drug was used in the Dental Department a preliminary investigation was carried out upon patients undergoing modified electroconvulsive therapy to determine the comparative strengths of methohexital and thiopentone. This anaesthetic lends itself to comparison since each patient can act as his own control and may receive six or more anaesthetics at intervals of a few days. Thiopentone and methohexital were injected slowly and as far as possible at a constant rate. The loss of the eyelash reflex was taken as an end point. The same anaesthetist administered all these anaesthetics. The results were not analyzed until the completion of the series to avoid subconscious variation on the part of the anaesthetist. Eighteen patients were given 75 anaesthetics. The average dose of thiopentone

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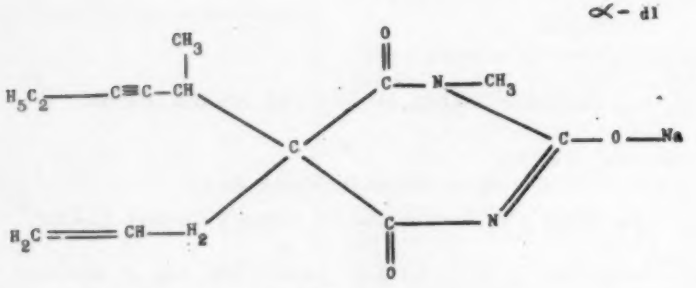

FIG. 1
Structural formula of methohexital sodium.

and the average dose of methohexital was calculated for each patient and expressed as a ratio. There was a fairly large variation in the highest and lowest of these ratios (from 4:0 to 2:1) but this was expected in such a method. The average ratio was 3:1 and this has been taken as a guide to the comparative strengths. Table I shows the result of this investigation.

TABLE I
The relative potency of methohexital and thiopentone.

Average dose thiopentone in mg	Average dose methohexital in mg	Potency of methohexital: thiopentone
400	130	3.08:1
400	100	4.00:1
375	140	2.68:1
350	115	3.04:1
350	116	3.02:1
333	120	2.78:1
317	95	3.33:1
310	95	3.26:1
300	100	3.00:1
275	100	2.75:1
275	100	2.75:1
250	70	3.57:1
250	70	3.57:1
250	70	3.57:1
250	105	2.38:1
250	120	2.09:1
250	90	2.77:1
250	105	2.38:1
237	85	2.79:1
237	97	2.44:1
237	110	2.16:1
235	80	2.47:1
225	75	3.00:1
225	72	3.13:1
225	80	2.75:1
225	95	2.37:1
187	80	2.34:1
	Mean	3.05:1

Standard deviation, 1.130. Standard error, 0.203. The potency of methohexital relative to thiopentone is therefore 3.05 ± 0.203 to 1.

Inevitably with any intravenous anaesthetic agent a comparison must be made with thiopentone as the standard, in view of the latter's widespread use and satisfactory service. With any new intravenous agent the danger is that low potency may be mistaken for short action. It is easy to be over enthusiastic about an agent when it is reduced quantity of active drug rather than short action which causes a rapid recovery. Buthalitone sodium was reported as having a shorter action than thiopentone but O'Mullane (1957) using the electroencephalograph was not able to support this. In view of O'Mullane's work, electroencephalographic recordings were made using methohexital and thiopentone. A dose of methohexital was given to volunteers while an electroencephalograph was recorded. On another day a comparable dose of thiopentone was given again with a continuous electroencephalographic recording. The patterns characteristic of barbiturate anaesthesia as described by Kiersey, Bickford and Faulconer (1951) were seen, with a short period of fast rhythm followed by slow wave forms. No definite conclusion could be drawn from the electroencephalograph with regard to differences in recovery time, as the fast rhythm faded into a normal rhythm without any abrupt change. It was noticeable, however, that with methohexital sleep the slow rhythm persisted for a longer period of time than with thiopentone. This presumably indicated that the depth of anaesthesia, as shown by these slower wave forms, lasted longer with methohexital. Despite this the recovery from methohexital sleep in these volunteers was clinically quite different. Following methohexital all volunteers were standing with no dizziness and

were ready to leave much sooner than following thiopentone (table II).

TABLE II

Subject	Time of slow wave form in seconds		Clinical time for full recovery in minutes	
	Metho-hexital	Thio-pentone	Metho-hexital	Thio-pentone
M.Y.	89	52	10	25
S.A.	92	47	15	50

INVESTIGATION IN DENTAL ANAESTHESIA

Technique.

The results based on 500 anaesthetics administered in the Dental Out-patient Department are reported. These were 284 adult female, 155 adult males and 61 children under 14 years of age. The youngest child was 5½ years old. The object was to obtain quiet dental anaesthesia without hypoxia and at the same time to achieve a rapid recovery. The patients were asked not to eat or drink anything for 4 hours before operation and to empty their bladders just prior to their appointment. No other pre-operative preparations were made.

Induction.

After examination of the mouth, a prop was inserted and methohexital was given intravenously as rapidly as possible. The dose decided upon after preliminary investigations was 5 mg per stone body weight. In young children slightly more methohexital was required in proportion to their weight. In order to conform with the conditions in the average dental surgery the patients were not weighed but their weight was assessed on their size and on information given. As soon as the patient was asleep, the nasal mask was placed over the nose and a mixture containing 15 per cent oxygen and 85 per cent nitrous oxide was administered. The time taken for sleep to ensue was between 17 and 20 sec. The nitrous oxide and oxygen mixture was delivered from a Walton machine with full pressure and the reservoir bag was turned off so as to eliminate rebreathing. A period of 1½ to 3 minutes was required to establish satisfactory conditions for operation in the majority of patients. At this stage, the oxygen percentage was increased to 20. To establish good operative conditions in the shortest time it was essential to have unobstructed nasal breathing. It was found that induction with methohexital gave very satisfactory results in this respect. The impression was gained that it is the smooth induction obtained when using methohexital which encourages nasal breathing, rather than any inherent characteristic of the drug. Systolic blood pressures were taken in 50 patients just after the onset of unconsciousness and again 3 minutes later. A transient fall of 5 to 10 mm Hg occurred in 60 per cent of this group. No fall or rise in pressure was found in 30 per cent. The remaining 10 per cent of patients all had systolic pressures above 170 mm Hg, and showed a maximum fall of 50 mm Hg.

Maintenance.

In only 15 patients was it found necessary to supplement the nitrous oxide with any other inhalation agent. In 9 of these nasal breathing was not easy to establish and trichloroethylene was used. In one patient ethyl chloride applied on a mouth pack was the only way to maintain anaesthesia in a persistent mouth breather. A further 5 patients required the use of trichloroethylene to establish smooth anaesthesia in spite of satisfactory respiration. A restraining strap was not used on any of the patients, although many were tough labourers. In only 45 (9 per cent) of the patients was any kind of restraint required.

A chairside spitoon was not provided and the patients were taken to another room for rinsing and spitting.

Recovery time (figs. 2, 3).

Two periods during recovery were recorded. These were: (1) the time from receiving the injection until the patient was capable of leaving the chair for the recovery room with the assistance of one nurse (fig. 2); the time from receiving the injection until it was considered that recovery was complete and that the patient could safely go home unaccompanied (fig. 3). The assessment of complete recovery was based on three main factors. These were: a co-ordinated gait; clear normal speech; absence of hangover. Absence of hangover was the final criterion for full recovery and was based on the answers to a number of standard questions: (*a*) Do you feel dizzy? (*b*) Does your head feel quite clear? (*c*) Do you feel quite normal? In the majority of patients it was observed that there was a fairly clear end

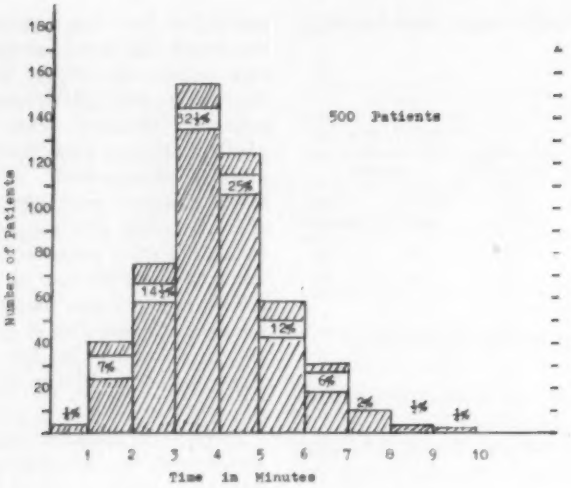

FIG. 2
The time from receiving the injection until the patient was capable of leaving the chair for the recovery room with the assistance of one nurse.

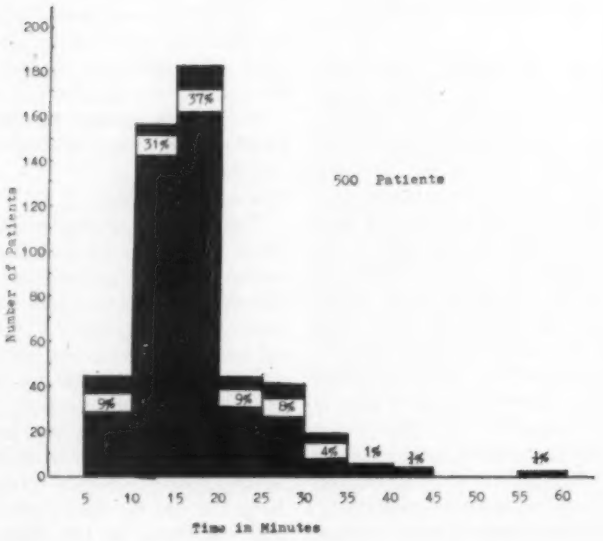

FIG. 3
The time from receiving the injection until it was considered that recovery was complete and that it was safe for the patient to go home unaccompanied.

point when they suddenly felt "clear" and "normal".

Ninety-four per cent of the patients were deemed fit to return home within half an hour and 77 per cent within 20 minutes. Only one patient caused any inconvenience. She refused to stand on her feet for an hour and had to be taken home in a car. She returned later for further extractions when nitrous oxide only was used. The same performance was repeated but it was slightly less prolonged.

Ninety-one per cent of the patients were able to leave the dental chair within 6 minutes of receiving the injection. In most of the other cases (9 per cent) the period of administration was longer than 6 minutes.

Reaction to the injection.

In order to obtain the patient's reactions to this type of dental anaesthesia, 100 consecutive patients were given a questionnaire (fig. 4) before leaving the clinic. They were asked to fill it in at home and post it back the next day. This enquiry was continued until 100 questionnaires had been returned. At this time 17 patients had failed to return their answers.

ROYAL FREE HOSPITAL
GRAY'S INN ROAD, W.C.1

Date.....

Serial Number .....

Name ..... Age..... Weight ..... Sex.....

Dose of C25398 ..... Time A ..... B ..... C ..... D.....

Remarks .....

QUESTIONNAIRE

		Please cross out words which do not apply	
1.	Have you had your teeth out under gas?	Yes	No
	If yes, do you prefer gas or injection?	Gas	Injection
2.	Did you find the injection unpleasant?	Yes	No
3.	Did you find going to sleep unpleasant?	Yes	No
4.	Did you find waking up unpleasant?	Yes	No
5.	If answer to 2, 3, and 4 is yes, please state why		
6.	Did you feel sick during recovery?	Yes	No
7.	Were you actually sick?	Yes	No
8.	Did you have a headache?	Yes	No
9.	Did you feel your teeth being pulled?	Yes	No
10.	Did you feel quite normal when you left hospital?	Yes	No
	If no, how did you feel?		
11.	Did you have to lie down or rest when you got home?	Yes	No
12.	Please add any personal remarks:		

FIG. 4

The questions were designed to find out the patient's personal response to this method of anaesthesia and to record any complications of recovery which might have occurred after leaving the clinic. They were invited to add any personal remarks which might be helpful.

The results of this questionnaire were favourable. Seven patients who had previously had nitrous oxide inductions for dental anaesthesia preferred that method to the methohexital for one reason or another. The majority of the remainder expressed their preference for the injection in enthusiastic terms. Sixteen patients felt the need to lie down on returning home; 13 of these were females, 1 was male and 2 were children. All except one of these patients, however, expressed their preference for this method. The rest of the patients were able to go straight back to their usual occupation. Two patients complained of feeling the extractions, although they made no complaint at the time. Five patients vomited during recovery and 14 felt nauseated but did not vomit at any time. Ninety-four patients said they felt quite normal when they left the clinic. Of the 6 who did not feel quite normal on the way home, 3 complained of feeling nauseated, 1 felt tired, 1 was dizzy and 1 felt faint. None of these patients had complained when seen prior to being given permission to go home.

DISCUSSION

In this investigation our main objective was to assess whether or not methohexital is a satisfactory and safe drug to use for dental anaesthesia in the chair. No attempt has been made to make a direct clinical comparison with any other intravenous drug or anaesthetic technique. Before commencing these trials it was necessary to carry out preliminary investigations in order to discover the relative potency of this drug as compared with thiopentone. The idea of using anaesthesia preceding electroconvulsive therapy to compare different barbiturates was first described by Egbert, Sechzer and Eckenhoff (1958). Their end point was lack of response to a command. In this investigation loss of the eyelash reflex was used. A considerable variation was expected and found, but the average ratio of 3:1, methohexital:thiopentone has since been supported by further clinical experience. It will be noticed that this ratio was different from the one found by Wyant and Chang (1959) but these authors used the dose per minute of anaesthesia, when the drugs were used for both induction and maintenance, as a criterion, whereas in this trial the drugs were used solely for induction. This difference in ratio would seem to agree with the fact that methohexital is shorter-acting so that more has to be used to maintain anaesthesia, when the ratio becomes smaller. When used for induction alone the length of action of each barbiturate is not taken into account.

The attempt to compare methohexital with thiopentone by investigating the electroencephalographic changes is open to criticism on the ground that not enough comparison is made with clinical findings and that alone the difference in wave form means little. Kiersey, Bickford and Faulconer (1951) have nevertheless described definite patterns to the electroencephalographic wave forms varying with the depth of anaesthesia. In this investigation the changing wave patterns during recovery were diffuse and gave us no useful information. However, the longer period of the slow wave pattern (Kiersey pattern 2) seen with methohexital was of considerable interest, as it coincided with the already formed clinical impression that methohexital gave deeper anaesthesia than thiopentone. The shorter recovery time, despite deeper anaesthesia, was a striking feature of methohexital anaesthesia as compared with thiopentone.

Wyant and Chang (1959) reported a high incidence of apnoea following induction of anaesthesia with methohexital. This did not occur on any occasion in our series, probably owing to the small dose of the drug used. Because of the difficulty in dealing with apnoea in the dental chair it is felt that it is most important that the induction dose should remain small. An additional small dose can be given during maintenance anaesthesia, if required, without the risk of prolonging the recovery time unduly.

The incidence of vomiting was encouragingly low. It is felt that 5 per cent is probably the irreducible minimum that can be obtained in the unpremedicated out-patient by any method.

Although the time taken to prepare the patients for dental extraction was longer than with pure nitrous oxide, the smoothness of the procedure

and the absence of hypoxia, more than compensated for this. Nine per cent of the patients needed some degree of restraint, but this was only to hold an arm or the knees together. None of the patients were reported as being violent and on no occasion was it necessary to alter the planned operation because of difficulty with the anaesthetic.

The patients seemed to welcome this type of anaesthesia. Ninety-three per cent preferred it to nitrous oxide and 47 per cent gave an enthusiastic voluntary appraisal.

Using the technique described, perfect conditions were obtained in over 90 per cent of the patients anaesthetized without subjecting them to any period of suboxygenation or having the inconvenience of a moving patient during the extractions. Yet the time required for complete recovery was conveniently short. Since a short recovery time is the main advantage hoped for in this drug and one of the most important features of any drug used for out-patient anaesthesia, a critical investigation on this point is being carried out. It must be remembered that until it can be established without reasonable doubt that the assessment of clinical recovery means a return to complete normality, all patients should be accompanied home and must not be allowed to drive cars or any other vehicle for several hours after anaesthesia.

SUMMARY

Some of the problems of dental anaesthesia are discussed.

An intravenous induction with 1 per cent methohexital, using a dosage of 5 mg/stone (6.3 kg), followed by nitrous oxide and oxygen, was given to 500 patients in the dental surgery. Particular attention was paid to the prevention of hypoxia. The technique is fully described.

Preliminary investigations were carried out on volunteers with e.e.g. recordings and also with e.c.t. anaesthesia when the ratio of strength of methohexital to thiopentone was 3.1 to 1.

In 15 cases nitrous oxide needed trichloroethylene as a supplement. In 45 cases some restraint was required. Ninety-four per cent of patients were able to return home within half an hour and 77 per cent within 20 minutes.

Apnoea was not found in this series, probably because of the low dose and the incidence of vomiting was only 5 per cent which was considered the irreducible minimum.

In 100 patients a 24-hour follow-up was carried out by means of a simple questionnaire which the patients were asked to fill in and return the following day. All but 7 per cent of the patients preferred this type of anaesthesia. The results are fully recorded.

Methohexital is considered to have great promise in dental anaesthesia, provided it is used solely as an induction agent and in the small dosage described. The anaesthesia is more smooth and satisfactory than with nitrous oxide-oxygen and the recovery is rapid, but the patients should be escorted home until further work has been carried out on the assessment of clinical recovery.

ACKNOWLEDGMENTS

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NITROUS OXIDE ANAESTHESIA FOR AMBULATORY PATIENTS*

BY

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THE object of this paper is to review some anaesthetic techniques, clinical observations and theoretical points which were considered while seeking a satisfactory method for the administration of nitrous oxide to ambulatory patients. Most of the personal observations described were made during anaesthetics which were administered in the casualty department of the Royal South Hants Hospital. For these a Boyle anaesthetic machine was used. Oxygen, nitrous oxide and cyclopropane were available for use in a Magill semiclosed system. Latterly the standard vaporizer bottle for trichloroethylene was replaced by a bottle calibrated by I.C.I. for halothane administration. For dental anaesthesia, an old Walton machine was used with a thick-walled reservoir bag in circuit. The nasal masks were fitted with Coxeter expiratory valves. A vaporizer calibrated for halothane administration was not available. All the anaesthetics administered in the casualty department were recorded in a notebook in as much detail as circumstances permitted, a stopwatch being used to observe times. Latterly a home-made apparatus was used to keep continuous record of respiration during anaesthesia. The pressure changes occurring in the anaesthetic circuit adjacent to the reservoir bag were transmitted to a thin rubber diaphragm. This was connected to a simple ink writer. The recording paper was propelled by clockwork which also actuated a one-minute time marker. An additional marker was used to indicate the times of incidents recorded in the notebook. Deflections of the pen were non-linear with respect to pressure change and full scale deflection was produced by a pressure of about 10 mm Hg under static conditions. In all the records obtained full deflection nearly always occurred during expiration but the overshoot due to the inertia of the system was not known. When using this apparatus induction of anaesthesia was preceded by inhalations of 100 per cent oxygen while securing an airtight seal between mask and face. The simultaneous administration and recording of anaesthesia in the dental outpatient department was not practicable.

A common technique of nitrous oxide administration and its modification following experience with pigmented patients.

The author was trained to induce anaesthesia in the casualty department with 100 per cent nitrous oxide until the onset of "regular respiration" and then to use a mixture of nitrous oxide and oxygen. The emphasis was more upon the maintenance of anaesthesia using nitrous oxide than upon the maintenance of adequate oxygenation. Experience of anaesthetizing pigmented patients in Jamaica led to a modification of this technique. It was found difficult to assess cyanosis through pigmented skin. Furthermore, many Jamaicans were so anaemic that concentrations of reduced haemoglobin sufficient to exhibit cyanosis were barely possible without dangerous hypoxia. There was also the possibility of precipitating a sickle cell crisis (Golding, 1956). To allow for these conditions, and to avoid excessive hypoxia, induction was started with 6 breaths of 100 per cent nitrous oxide and continued with 2 litres of oxygen and not more than 10 litres of nitrous oxide per minute. If anaesthesia was still inadequate, trichloroethylene was introduced as a supplement.

The dangers of hypoxia.

The dangers of hypoxia during anaesthesia have been emphasized. Bedford (1955) observed that in a group of 1,193 patients over the age of

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50 years who had had operations, 120 showed some degree of mental deterioration, while 29 had become demented. Discussing hypoxia as a possible cause, he mentioned the occasional catastrophic effects of anoxia during nitrous oxide anaesthesia, which had been vigorously emphasized by Courville (1955) and by Bourne, J. G. (1952). Bourne stressed the inevitable hypoxia associated with brief nitrous oxide anaesthetics and quoted Macintosh as having knowledge of five deaths, within as many months, due to the effects of such hypoxia upon the myocardium. Bourne, J. G. (1957) has also remarked upon the hazard of fainting in the dental chair. Bourne, W. (1936) has shown that hypoxia may produce reversible yet undesirable damage, such as that suggested by the impairment of hepatic function produced by nitrous oxide with cyanosis

The partial pressures of oxygen in anaesthetic mixtures compared with those in air at various altitudes.

Hypoxia occurring during nitrous oxide anaesthesia may be put into perspective by relating given mixtures of nitrous oxide and oxygen, inhaled at sea level, with the altitudes at which atmospheric air would contain the same partial pressures of oxygen. For example, the mixture of 2 litres of oxygen with 10 litres of nitrous oxide per minute, described above for the maintenance of anaesthesia, allows for a minimum inspired oxygen concentration of 16.7 per cent. The partial pressure of this corresponds with that in air at 6,000 feet.

The relationships between anaesthetic mixtures at sea level, partial pressures of oxygen and altitude are indicated in figure 1. This has been derived from tables (Dittmer and Grebe, 1958). It can be seen that in a mixture of 10 litres of nitrous oxide with 1 litre of oxygen (or 9 per cent oxygen), the partial pressure of oxygen is the same as that in air at an altitude of 22,500 feet. At this height above sea level even the fittest of acclimatized mountaineers become dyspnoeic upon the slightest exertion. A patient inspiring such

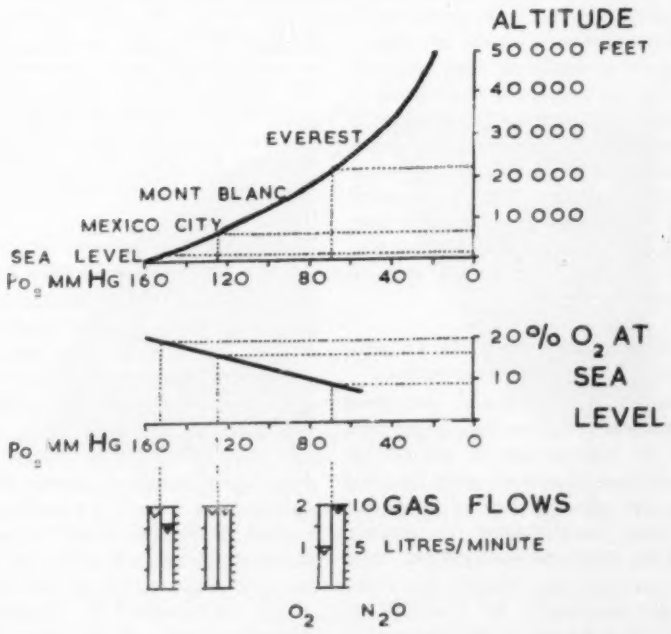

FIG. 1

Altitudes at which the partial pressure of inspired oxygen would be the same as that of given nitrous oxide and oxygen mixtures at sea level.

a mixture during anaesthesia would also be subjected to the resistances of an anaesthetic circuit, in particular to that of the expiratory valve. To what height would it be reasonable suddenly to project a patient with whom one has made only the briefest acquaintance, within whom may lurk unsuspected disease, and whose physiological powers of adaptation may be limited?

The induction of "amnalgesia" using 100 per cent nitrous oxide.

With the object of avoiding the hazards of hypoxia, Tom (1956) applied what Klock (1951, 1955) had earlier described as "amnalgesia" to anaesthesia for dental extractions. In Tom's technique induction is commenced using a few breaths of 100 per cent nitrous oxide and is then continued with 15 per cent oxygen. The state of "amnalgesia" is produced after about 40 breaths, and is often preceded by a hesitation in breathing. (Tom claimed to correct this by verbal encouragement to "keep blowing.") Breathing then becomes free and regular and after a few more breaths the patient is ready. Dental extraction is accompanied by some movement and occasionally by phonation. This technique is similar to that described above and used by the author for anaesthesia in the casualty department, except that Tom did not describe the use of supplementary agents, such as trichloroethylene. In practice the technique may permit more hypoxia than might be expected to occur during the maintenance of anaesthesia with 15 per cent oxygen, since the calibration of apparatus used in dental departments may be grossly inaccurate (Bourne, 1960).

The induction of anaesthesia using 100 per cent nitrous oxide following pre-oxygenation.

Whereas Tom sought to avoid dangerous hypoxia by administering not less than 15 per cent oxygen during the maintenance of anaesthesia, Mostert (1958) claimed to achieve safety by using pre-oxygenation. He affirmed that 85 to 90 per cent nitrous oxide was required to produce anaesthesia and that 20.93 per cent oxygen could not be allowed for short anaesthetics. He therefore advocated pre-oxygenation for 2 minutes in order to replace 98 per cent of the nitrogen in the lungs by oxygen and so provide a reserve of oxygen to cover the period of nitrous oxide induction. Following pre-oxygenation 100 per cent nitrous oxide was given for 1 minute at a flow rate greater than the patient's assumed minute volume. This was stated to provide adequate anaesthesia within the next half-minute. Breath-holding was said to be rare. For 15 to 30 seconds, while the surgeon started, 10 to 15 per cent oxygen was administered. This was followed by 20 per cent oxygen. Supplementary agents were added if the operation lasted for more than 2 to 3 minutes.

Considering the many differences between patients, the set time of 1 minute for 100 per cent nitrous oxide inhalation seemed too rigid. An alternative suggested itself in the administration of 100 per cent nitrous oxide for as long as the patient would respond, by nodding, to the anaesthetist counting aloud each breath taken (see "Loss of consciousness, amnesia and analgesia" below). This was tried once.

Case history.

The patient was a tall active female of 67 years, requiring reduction of a Colles fracture. She nodded in response to the counting aloud of 25 breaths during induction, but at this stage cyanosis was detected. It was realized afterwards that those 25 breaths had taken nearly 2 minutes. Gas flows were then altered to 6 litres of nitrous oxide and two litres of oxygen per minute. There was a short period of apnoea but cyanosis soon disappeared as respiration resumed. Respiration then became obstructed and an airway was inserted. The conditions for operation were excellent. The management of anaesthesia could have been much safer.

The latent period between the inhalation and the action of an anaesthetic agent.

One obvious factor overlooked in the above reasoning was the delay between the inhalation of a gas, its transport in solution and its effective action upon the central nervous system. To investigate this, 15 patients, of average age 38 years, were asked to signal, by raising a hand, the very first onset of subjective change after inhaling a single deep breath of nitrous oxide. The delays ranged from 15 to 55 seconds and averaged 32 seconds. These figures may be compared with the figure of 35 seconds given by Wylie (1953) as the time taken for 75 per cent nitrous oxide with oxygen to become fully effective when used in midwifery; and with the 12 to 15 seconds given by Guedel (1953) as the time of passage of blood from the lungs to the brain. The author experi-

enced a delay of 20 seconds between taking a single breath of nitrous oxide and noting any subjective effects. This was consistent with the half-dozen breaths actually counted before appreciating any change during a nitrous oxide induction (see below). No subjective effects followed the inhalation of a single deep breath of 100 per cent nitrogen.

A comparison of induction techniques using nitrous oxide without and with pre-oxygenation.

Apart from the knowledge of the composition of gases inhaled by the patient, the only clinical guide to alveolar oxygen tension in a normal patient is peripheral cyanosis. If it be accepted that cyanosis is indicative of excessive hypoxia, then there is no clinical warning of its approach during a nitrous oxide induction. Since measurement of breath-by-breath alveolar composition is not practicable during anaesthesia in outpatient departments, an attempt has been made to calculate approximate values that might be expected to occur during the induction of a hypothetical patient by each of two techniques. The results are shown in figure 2. Allowance has been made for the dilution of 3,000 ml of functional residual air with an effective tidal volume of 300 ml at a respiratory rate of 15 per minute; for the solution and transport away from the alveoli during each respiratory cycle of 20 ml of oxygen plus the volume of nitrous oxide calculated to be soluble in one-fifteenth of a cardiac output of 5,000 ml per minute, at the calculated prevailing partial pressure (blood/gas partition coefficient was taken as 0.47); and for the replacement of these dissolved gases by carbon dioxide and dead-space gas from the previous expiration. The figures chosen and calculated may have a very doubtful relationship with the true state of affairs existing in any given patient, but they should give some idea of the relative orders and patterns of change in alveolar composition when the techniques of Tom and Mostert are used. The results suggest that there is a greater margin of safety after pre-

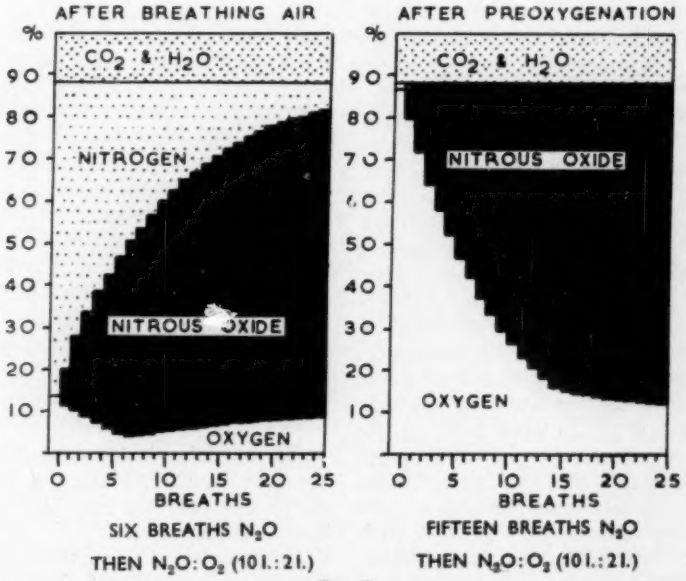

FIG. 2

See text. Calculated breath-by-breath alveolar gas concentrations during induction of nitrous oxide anaesthesia, in a hypothetical patient, by two techniques.

oxygenation. When induction is started with six breaths of 100 per cent nitrous oxide without pre-oxygenation hypoxia may contribute to loss of consciousness, especially in those patients with whom contact is quickly lost (see "Loss of consciousness, amnesia and analgesia" below). The justification for this short period of hypoxia is open to question.

Loss of consciousness, amnesia and analgesia.

The author has personally experienced an induction by Tom's technique for a dental extraction.

From the start the author counted each breath to himself. A subjective change was noted at the 6th or 7th breath. At the 12th breath the anaesthetist was heard to say, "He seems to be taking it all right". At the 13th breath there was cerebration to the extent of realizing that 13 was an "unlucky number", of calculating that twice 13 was 26 and of wondering whether breaths could be counted up to that number. In retrospect there was no memory of counting beyond 13. Upon recovery there was an awareness of an indistinct figure who clarified into the anaesthetist. The author was soon feeling fully awake, standing up and asking how long it had taken. Before this, however, he had apparently asked the anaesthetist, "Who are you?" Of this there is no memory. He had then made an exclamation which cannot be remembered with certainty. Was the author still unconscious at this time and talking like someone talking in his sleep, or was he subsequently just amnesic?

Following this experience, breath counting was used to find out when patients lost consciousness during induction of nitrous oxide anaesthesia. Each breath taken by the patient was counted aloud by the anaesthetist and the patient was asked to nod slightly in response. Upon recovery enquiry was made of the last count heard. Figure 3 shows the results arranged from above downwards in order of the number of nods observed. Each horizontal stick represents an anaesthetic. Its length indicates the number of nods observed by the anaesthetist and the black portion indicates the number of nods remembered by the patient. There was much variation. On average just over half the nods were remembered. Counts were not always definite. Some patients stopped nodding early but resumed on command. Nodding sometimes became unrelated to counting. Some patients began shaking their heads instead of nodding and occasionally nodding became so exaggerated as to require restraint. The last number remembered was not always definite, a lower figure often being given soon after return to consciousness than could be given later. That patients were in fact responding to the spoken voice and not nodding automatically with respiration was sometimes checked by asking them to shake the head instead of nod. Compliance with this request was variable and noncompliance was of uncertain significance, as shown by the following example.

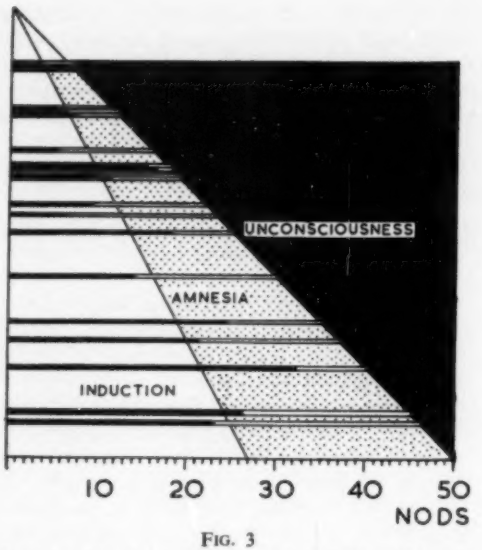

FIG. 3

See text. Number of nods made by 20 patients in response to the anaesthetist counting aloud each breath taken during induction of nitrous oxide anaesthesia.

Case history.

An engineer of 44 years nodded 25 times. The later nods looked automatic. He did not comply with the request to shake his head. Other observers considered that he had responded satisfactorily to only 21 or 22 counts. In fact he not only remembered counts up to the 25th, thereby demonstrating negligible amnesia, but he also remembered being asked to shake his head. He could not explain why he had not done so.

Any hesitation in breathing that occurred was always noted after the last nod. It seems unlikely that exhortations to "keep blowing" would have made any difference.

If this experiment were to be repeated with the lower partial pressures of nitrous oxide commonly used in abdominal and thoracic surgery, it might be found that we are more often "amnalgetists" than anaesthetists. Indeed, Gray (1954) and Rosen

(1959) have made relevant observations. Gray described a level of narcosis at which subjects obey commands yet afterwards assert that they have been unconscious. He also found that onset of analgesia was close in time to loss of consciousness. Rosen was able to establish contact, in some instances, with patients stabilized on being given nitrous oxide and oxygen mixtures containing up to 73 per cent nitrous oxide. Almost half the patients with whom good contact was made had total amnesia.

The late onset of analgesia referred to by Gray had been suspected from observation of those patients in the casualty department who had preoperative pain. Relief from pain during induction of anaesthesia was denied by headshaking even when attempts were made to ameliorate the pain by suggestion. Although Chapman, Arrowood and Beecher (1943) concluded that 20 per cent nitrous oxide with oxygen had an analgesic potency equivalent to morphine 16 mg against pain produced by radiant heat and ischaemia, this effect took 10 minutes to reach maximum. "Gas" and hypoxia, however, are still combined in midwifery in the use of self-administered gas and air.

The use of supplementary agents.

The indications for the use of particular gas mixtures and supplementary anaesthetic agents vary with the anaesthetist. An examination of the casualty operations register at the Royal South Hants Hospital was made to ascertain how frequently nitrous oxide and oxygen mixtures were in fact administered with and without supplementary agents. Over a 17-month period 45 per cent of 1,259 nitrous oxide anaesthetics were administered without the use of supplementary agents. A more detailed analysis was made of a group of 131 personally administered anaesthetics, 48 per cent of which were not supplemented. Anaesthetics were given twice as often for bone and joint surgery as for scissions and sutures, but supplementation of nitrous oxide was required twice as frequently for the latter as for the former. This was presumably related to the intensity and duration of the surgical stimuli, and perhaps also to ease of restraint. The greatest incidence of bone and joint surgery was in the early and later years of life. The early years involved males more than females and the later years females more than males. Those patients who were over the age of 50 years were more easily anaesthetized by nitrous oxide and oxygen alone than those below this age. The incidence of scissions and sutures declined steadily with increasing age.

Walsh (1958) described the use of halothane as a supplement to nitrous oxide anaesthesia for dental extractions. Subsequently he introduced it to the casualty department of the Royal South Hants Hospital. Previously trichloroethylene had been the most favoured supplementary agent. A technique tried by the author latterly was to induce anaesthesia with 8 litres of nitrous oxide and 2 litres of oxygen per minute with 0.15 to 0.3 per cent halothane. The halothane administration was then stopped, maintained or increased according to the reaction of the patient to surgical stimulation. The cost of using halothane in the casualty department was about two shillings per-anaesthetic. Impressions from brief experience with this technique suggest that induction is not unpleasant and that it takes about 5 minutes. Loss of consciousness appears to be rapid after allowing for the delay between first inhalation and effective action. Restraint may be needed in the early stages but relaxation soon follows. There may be some movement upon surgical stimulation. Return to consciousness is a little slower than after nitrous oxide and oxygen anaesthesia. The time at which recovery is complete is difficult to assess but it appears to be much later. The ears remain flushed and nystagamus may be observed even after the patient has risen from the table and professed to be fully recovered.

The following case report provides a warning about the use of this particular technique for patients in the dental chair.

Case history.

A tall, fit, tough welder in his early twenties attended for dental extraction with a note to the effect that it was not possible to anaesthetize him with nitrous oxide. The halothane technique was tried using an uncalibrated vaporizer. The anaesthetic appeared to be entirely satisfactory. The patient recovered consciousness quickly, smiled and expressed surprise and pleasure at the ease with which the operation had been carried out. Shortly afterwards he slumped in the dental chair and lost consciousness. He was pink. His superficial temporal pulse was still palpable but rather slow and of low tension. He was placed in a horizontal position, whereupon he repeated the performance of waking up, smiling, talking, sitting up and slumping. After being kept horizontal for a period there was no further trouble.

CONCLUSION

An ideal anaesthetic for an ambulatory patient should please the patient, the surgeon and the anaesthetist. It should have a high margin of safety and recovery should be complete and immediate. These requirements would seem to be most nearly met when the least hypoxic nitrous oxide and oxygen techniques prove adequate without supplementation using more potent drugs, but this requires more patience than when hypoxic methods are used. If supplementary agents are needed they should be used sparingly.

SUMMARY

Some techniques for inducing and maintaining nitrous oxide anaesthesia are reviewed with particular reference to the oxygen content of inspired and of alveolar gases. A method of recording observations during such anaesthesia is mentioned. The use of supplementary anaesthetic agents is considered.

Attention is drawn to the variable latent period between the inhalation of an anaesthetic agent and the onset of subjective effects.

A breath-counting technique for assessing the time of loss of consciousness and of amnesia is described and reference is made to the circumstances of analgesia, amnesia and loss of consciousness.

The register of anaesthetics administered in a particular casualty department is examined with particular regard to the use of supplementary agents in relation to the type of surgery performed and the age and sex of the patients.

ACKNOWLEDGMENTS

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FOUR YEARS' EXPERIENCE WITH HEXAMETHYLENE-1.6-BISCARBAMINOYLCHOLINE (IMBRETIL) AS A MUSCLE RELAXANT

BY

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THE addition of a second carbaminoyl group to the carbaminoylcholine molecule results in compounds which block neuromuscular transmission. In contrast to suxamethonium, these are not split by serum cholinesterases. One of these substances which showed promising qualities as a muscle relaxant has been introduced into clinical practice under the name of Imbretil. It is characterized by the interposition of an aliphatic chain of six methyl groups between the carbaminoyl groups.

Imbretil is longer acting than d-tubocurarine and more potent than decamethonium. In spite of some favourable reports (Brücke and Reis, 1954; Holzer, Waltner and Willomitzer, 1954; Reis, 1955), the use of such a long acting depolarizing relaxant has met with some criticism. Several authors have shown that neostigmine given at the end of operation restores spontaneous respiration (Meissner, 1957; Bergmann, 1958; Mayerhofer, 1958; Krüger, 1958), although at first this was not expected in view of the depolarizing character of Imbretil. Other studies, however, have shown that neostigmine is not a reliable antidote, at least in the first phase of the Imbretil action (Foldes, 1959 et al.; Dripps et al., 1959; Ngai et al., 1959).

During the past four years, we have used Imbretil in over 2,500 cases in such a manner that we seldom required an antidote. Most of these operations lasted longer than 45 minutes and this required an extended period of relaxation. This paper is a report of our methods and experience.

In clinical practice, several different schemes of dosage are possible. A single large dose may be injected to produce sufficient relaxation for the whole operation. If necessary the action may be antagonized at the end of the operation by neostigmine. The required dose may be determined in advance with fair accuracy, according to body weight and duration of operation. However, difficulties may be encountered should the operation end before the expected time. Alternatively, small repeated injections may be made (0.5–1 mg) to build up and maintain the required degree of relaxation. In a third method, a single dose may be given sufficient to produce apnoea for about half the time of operation. In longer operations this dose (for example 4–5 mg for a gastrectomy) will be sufficient for intubation. Towards the end of the operation the fading action of Imbretil can easily be augmented with very small amounts of suxamethonium to secure total relaxation. While we consider that the use of Imbretil is mainly indicated in relatively long operations, it is possible to give a small dose of 1–2 mg as a basic relaxant, in shorter procedures, having used suxamethonium for intubation.

In our experience this third method has several advantages. Imbretil as a long acting and suxamethonium as a short acting relaxant have the same mechanism of action. The relaxation can be controlled optimally without a continuous intravenous drip. The total dose is very small.

When d-tubocurarine is used, atropine and neostigmine are necessary in most cases. These drugs are not entirely free from danger. After the use of the combination of Imbretil and suxamethonium no antidote has been required in at least 95 per cent of our patients. Neostigmine seemed to be an effective antidote in the few cases of prolonged apnoea.

Imbretil causes no histamine release in clinical doses and is free from side effects on the vegetative system and circulation, apart from a transient flush similar to that which may appear after suxamethonium. It can be combined with all the commonly used narcotics. When halothane is used at the same time, the collapse described when this

agent is used with d-tubocurarine does not occur. In our experience, the combination with halothane is especially advantageous as with relatively low doses of Imbretil it is possible to control respiration.

The solution of Imbretil is stable, does not precipitate with other drugs and is very economical.

TECHNIQUE

The night before operation a barbiturate is given. One and a half hours pre-operatively pethidine 50–100 mg with atropine 0.5 mg and, in some cases, promethazine 50 mg are injected intramuscularly. During the first two years a few patients also received chlorpromazine, 25 mg intramuscularly.

Anaesthesia is induced with thiopentone and this is quickly followed in most cases by a single injection of Imbretil, usually before intubation. In most cases anaesthesia is maintained with controlled ventilation, using nitrous oxide, 1,000 ml/min and oxygen 600 ml/min in the closed circuit, frequently with the addition of halothane, ether or cyclopropane and, in a few cases, pethidine. Further doses of Imbretil are given if the initial dose is found to be too small at the beginning of the operation, or if the operation lasts longer than expected. Body weight, general condition and the expected duration of operation are the main factors to be considered in assessing the dose of Imbretil so that spontaneous respiration will return by the end of the operation.

When relaxation is required late in the operation as, for example, during the closure of the abdominal wall, either small single doses of suxamethonium are given, or the anaesthesia is deepened. With increasing experience we have learned to produce optimal conditions with only 3 to 5 mg doses of Imbretil in practically all operations.

RESULTS

In table I the patients are classified according to the type of operation performed. We used Imbretil in patients of all ages except those in early infancy, in whom a long-acting relaxant was not required. Thus the age groups (table II) correspond to the frequency of the given operations at certain ages. As the use of different anaesthetic agents influences the amount of relaxant required, the entire medication given to the last 30 unselected cases undergoing various surgical procedures are summarized in tables III–VIII. Table III shows the drugs used in 30 cases of gastric resection.

TABLE I
Nature of surgical procedures

1. ABDOMINAL SURGERY	
Gastrectomies (including total gastrectomies)	426
Cholecystectomies and operations on the bile duct	541
Splenectomies	79
Gastroenterostomies, gastrotomies and perforated ulcer	78
Pancreatic resections and pancreatectomies	9
Portocaval anastomosis	7
Extirpations of the rectum (abdominoperineal)	68
Hemicolectomies and other intestinal operations	182
Secondary appendicectomies	11
Exploratory laparotomies and other minor intra-abdominal surgery	107
2. THORACIC SURGERY	
Resections of oesophagus or cardia	57
Lung resections	205
Mitral commissurotomies	136
Heart operations in hypothermia	38
Pericardectomies	32
Coarctations and Blalock's anastomosis	65
Diaphragmatic hernia	31
Mediastinal tumours, decortications of lung and exploratory thoracotomies	108
3. Surgery of the kidney, ureter and bladder	288
Prostatectomies	23
Incisional hernia and omphalocele	60
Lumbar sympathectomies	13
Resection of the ribs, thoracoplasty	17
Thyroidectomies	22
Mastectomies	20
Surgery on the trunk and the pelvis	11
Surgery on the extremities	26
Miscellaneous	34
Total	2694

TABLE II
Age distribution in 2,694 cases.

0– 9 years	49
10–19 ,,	132
20–29 ,,	312
30–39 ,,	392
40–49 ,,	486
50–59 ,,	730
60–69 ,,	468
70–79 ,,	118
80 and over	7
	2694

TABLE III

The requirement of drugs during gastric resections. Average values in 30 unselected patients.

	Male (24)	Female (6)
Age (years)	57.2	50.8
Weight (kg)	71.8	49.0
Duration of operation (min)	110	
Thiopentone (total) (mg)	418	366
Halothane (ml)	5.6 (in 22 cases)	
Imbretil (total) (mg)	4.81 ± 0.74*	2.8 ± 0.72*
Suxamethonium (mg)	88.3 (22 cases)	88.3 (6 cases)

* Standard deviation.

None of these patients received an antidote. One patient left the operating room with the endotracheal tube in situ, but all the others were awake and had full spontaneous respiration at the end of the operation. For intubation in 18 of these 30 cases we used Imbretil as the only relaxant. Suxamethonium was used in addition in 12 patients, the average dose being 63 mg (the table does not include this dose used only for intubation.) Patients suffering from carcinoma of doubtful operability received Imbretil only in small doses as a basic relaxant until it was certain that the condition was operable.

In biliary surgery (table IV) we do not exceed a total dose of 3 mg in women and 4 mg in men. Suxamethonium in small doses was used to secure complete relaxation if necessary, for example, during intubation and for opening and closing the abdominal wall.

Table VII gives details of 30 cases of commis-

TABLE IV

Average values in 30 patients undergoing operation on the gall bladder and bile ducts.

	Male (8)	Female (22)
Age (years)	55.3	49.7
Weight (kg)	75.3	61.8
Duration of operation (min)	93	70
Thiopentone (total) (mg)	363	401
Halothane (ml)	5.4 (in 19 cases)	
Imbretil (mg)	3.2 ± 0.64	3.02 ± 0.5
Suxamethonium for intubation (mg)	46.5 (in 7 cases)	73.3 (in 6 cases)
Suxamethonium during operation (mg)	57	46
Neostigmine (mg)	—	—

One patient left the operating room with a nasal tube in position.

TABLE V

Average values in 30 cases of extirpation of the rectum (abdomino-perineal) (26 male and 4 female).

Age (years)	51.7
Weight (kg)	70.3
Duration of operation	160 min
Thiopentone (mg)	652.5
Halothane (ml)	8 (in 5 cases)
Imbretil (mg)	3.51 ± 0.9
Suxamethonium for intubation (mg)	58.0 (in 24 cases)
Suxamethonium during operation (mg)	55.5 (in 24 cases)

No cases required antidote.

TABLE VI
Average values in 30 cases of resection of the lung.

	Male (19)	Female (11)
Age (years)	43.5	30.5
Weight (kg)	69.4	56.6
Duration of operation	150 min	190 min
Thiopentone (mg)	534	530
Halothane (ml)	7.7 (in 9 cases)	
Ether (g.)	25 (in 1 case)	
Pethidine (mg)	100 (in 3 cases)	
Cyclopropane	in 1 case	
Imbretil (total) (mg)	4.2 ± 0.3	4.1 ± 0.5
Suxamethonium for intubation (mg)	50 (in 7 cases)	
Suxamethonium during operation (mg)	95 (in 25 cases)	

In 9 patients in this series a further 1 mg dose of Imbretil was injected. This is included in the figures above.

surotomy of the mitral valve. There were 23 females and 7 males. It shows that, just as in other thoracic operations, it is easy to secure optimal conditions during the whole procedure by means of a single injection of Imbretil together with small doses of narcotics.

During operation one patient was given pethidine 40 mg. At the end of operation all patients were conscious with adequate spontaneous respiration except one. This patient, a woman of 47 kg, who had received Imbretil 4 mg required neostigmine 0.5 mg as an antidote.

Average values for 30 heart operations with interruption of the circulation are shown in table VIII. The majority were cases of atrial septal defect or pulmonary stenosis. Surface cooling with ice was used and patients were rewarmed by means of rubber blankets. Premedication varied, but no phenothiazine was used. Anaesthesia to Stage III, planes 1 and 2 (Guedel) was produced with ether.

TABLE VII
Average values for 30 cases of mitral commissurotomy.

Premedication: promethazine	35 mg
pethidine	75 mg
atropine	0.2 mg
Age (years)	36
Weight (kg)	59.7
Duration of operation (min)	97
Thiopentone (mg)	270
Halothane (ml)	4.6
Imbretil (mg)	3.9
Suxamethonium (mg)	42 (in 6 cases)

From this data it is evident that all patients had spontaneous respiration at the end of operation. In only a few cases was the endotracheal tube left in position after this, until relaxation was completely abolished. With increasing experience, neostigmine was found to be superfluous.

Apart from its use in anaesthesia, Imbretil is very useful in the treatment of tetanus. A single intramuscular injection provides relaxation of long duration, hence one is not dependent upon the unreliable absorption of depot preparation of tubocurarine or an intravenous drip. We use single doses of 1 to 3 mg at intervals of 1 to 4 hours, depending on the age of the patient, the severity of the convulsions and whether spontaneous or controlled respiration is indicated.

MODE OF ACTION OF IMBRETIL IN MAN

The mode of action of Imbretil in man was investigated by stimulating the ulnar nerve and recording the electrical activity of the muscle and the mechanical contraction simultaneously. The results of this work will be published later in detail (Schmidt, 1960). Summarized they are as follows.

After an intravenous injection of 1 mg the maximal paralysis was reached in 8 to 10 minutes and disappeared spontaneously after about 30 minutes.

The intravenous injection of 0.5 to 1 mg doses of neostigmine at the point of maximal action abolished the paralysis within 10 minutes in most cases. However it was not always possible to differentiate between this action and spontaneous recovery.

TABLE VIII

Average values for 30 operations on the heart with circulatory interruption.

Age (years)	17
Weight (kg)	43.8
Duration of anaesthesia (including rewarming)	7 hrs/27 min
Thiopentone (mg)	270 (in 22 cases)
Cyclopropane induction	in 24 cases
Ether (g.)	64.3
Imbretil (mg)	3.1
Suxamethonium for intubation (mg)	44 (in 5 cases)
Suxamethonium during operation (mg)	42 (in 6 cases)

Antagonism was more significant and reliable if neostigmine was injected at a later stage—e.g. 1 to 1½ hours following the injection of a higher dose of Imbretil such as 3 to 5 mg. In most of these cases the dose of neostigmine required to produce antagonism did not exceed 0.5 mg intravenously.

Small doses of methylcurarine abolish the effect of 0.5 to 1 mg Imbretil and vice versa.

Imbretil and suxamethonium intensify each other's action at all times and in all doses, no matter what the sequence of injection.

DISCUSSION

The mechanism of action of Imbretil is a dual one. On one hand the drug is a depolarizing relaxant. Intravenous injection is followed by muscle fibrillation, which is less marked than that following suxamethonium and does not lead to myalgia. Imbretil liberates potassium ions from skeletal muscle and causes contraction of the tibialis muscle of the pigeon (Klupp et al., 1953). On the other hand, in cats Imbretil causes a decrease in the endplate potentials (Pillat et al., 1955). The endplate potentials are at least partly restored by neostigmine, which also antagonizes paralysis of the gastrocnemius in rats. Imbretil is eliminated relatively slowly by the kidneys. Other possible means of elimination are unknown. The action-duration curve shows a slope after a steep rise.

Following the injection of Imbretil 4 mg, intubation is possible with the glottis widely open within 3 to 4 minutes. Adequate spontaneous respiration returns within 30 to 40 minutes although of course there is still an evidence of residual relaxation. It is possible to control respiration by slight hyperventilation for 30 minutes or longer.

While the residual relaxation persists, care must be taken to maintain a free airway. Further injections of Imbretil during the period when spontaneous respiration is returning lead to considerable residual paralysis. At this stage ⅓ to ¼ of the initial dose is sufficient to double the length of apnoea.

SUMMARY

Imbretil has been used successfully to produce relaxation in 2,700 cases of major surgery over a period of 4 years. In most cases the dose given was so small that the effect had worn off by the end of the operation. If necessary small doses of suxamethonium may be given safely during the latter part of the operation to secure complete relaxation. Thus relaxation can be controlled efficiently without the use of an intravenous drip.

A technique is described with which an antidote is seldom required. Neostigmine has proved an effective antidote in occasional cases of overdosage.

Imbretil has no side effects. It is economical and can be combined with all narcotic agents.

Some investigations concerning the mode of action of Imbretil are discussed.

ACKNOWLEDGMENT

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Brit. J. Anaesth. (1960), 32, 613

THE RISK OF EPIDURAL BLOCK IN OLD PEOPLE

BY

J. W. MOSTERT

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THE following case is identical to that reported by Morrow (1959) in that the high spread became manifest some 40 minutes after apparently perfectly administered epidural block. Morrow, however, assumed that in some unexplained manner intrathecal spread must have occurred. In the present case, nevertheless, the writer was able to establish both clinically and chemically that, in spite of small doses, total spinal blockade after epidural injection need not necessarily indicate spread via abnormal pathways such as the subarachnoid space, intraneural injection or both.

CASE REPORT

The patient was, like Morrow's case, a diabetic male of 70. He was 166 cm (5 ft. 5½ in.) tall and weighed 65 kg (143 lb.). His resting blood pressure was 180/110.

First anaesthetic. Epidural analgesia was induced for left lumbar sympathectomy with a 22 S.W.G. needle. Ten minutes after the injection of the test dose (and after a total of 22 ml 2 per cent lignocaine with 1 in 200,000 adrenaline) between L3 and L4 vertebrae the patient suddenly developed aphasia and apnoea associated with lively action of the neck and facial muscles. Artificial respiration was performed after endotracheal intubation, and a noradrenaline infusion maintained his usual blood pressure, except for one minute during the closure of the wound when cardiac arrest occurred. About five forceful inflations with oxygen with all the expiratory valves closed restored small pupils and palpable pulses. The blood pressure returned to its previous level as soon as the positive pressure was released. (This indirect method of cardiac massage (Keéri-Szanto and Rinfret, 1957) certainly resulted in no harm such as interstitial emphysema in this case.) The patient regained consciousness soon after, and electrocardiographically there was no evidence of recent myocardial damage.

Second anaesthetic. Two weeks later the patient required the amputation of his gangrenous toes. He again preferred regional analgesia; for its probable therapeutic value, and assured safety with liminal volumetric dosage, lumbar epidural analgesia was chosen. Premedication was light, being with 50 mg pethidine and 0.65 mg atropine.

1.30 p.m. With the patient sitting because of his constricted interlaminar spaces, a 20 gauge needle was inserted as before between vertebrae L3 and L4. The loss of resistance test was conclusive and the test dose of the same analgesic was injected. Repeated aspiration and testing for efflux, including the tasting of a few constantly bitter drops issuing from the needle, confirmed the accurate location of the point.

1.35 p.m. Another 12 ml analgesic was injected uneventfully.

1.50 p.m. Numbness of the feet was now present, but no weakness. The blood pressure was 160/100 and the operation was commenced.

2.05 p.m. The operation was over and the patient conversing animatedly. The blood pressure, however, fell rapidly to 100/85 at this time, and desoxyephedrine 15 mg was given intramuscularly and 7.5 mg intravenously. On command the patient moved both legs briskly.

2.15 p.m. The respirations became jerky and so shallow that cyanosis appeared. The blood pressure slowly rose. The trachea was intubated under direct vision. The vocal cords were seen to be active on laryngoscopy, and during intubation all the extremities and the facial muscles moved. Artificial respiration with oxygen was performed without the slightest resistance from the patient. The blood pressure remained above 170/100 without further vasopressor therapy. Later it was found that there had been amnesia for the whole period during which the endotracheal tube was in situ.

2.50 p.m. Adequate spontaneous respirations reappeared, and the patient was turned into the lateral position for aspiration of about 25 ml cerebrospinal fluid. The lignocaine content of this specimen was determined and found to be of the order of 50 parts per million.

3.05 p.m. The patient again complied with all commands including instructions to lift his legs. Although he could not manage to swallow, extubation was carried out.

3.45 p.m. The patient was now using his voice normally and appeared quite well. He subsequently remained so.

DISCUSSION

The 17 ml 2 per cent lignocaine used in this case contained 340 mg of the analgesic—roughly seven times the amount clinically used for subarachnoid administration. It follows that if in this case subarachnoid penetration had occurred of more than one-seventh the total volume injected, total paralysis of the lower extremities would have been inevitable. This did not occur, although Bonica (1958) considers 2 per cent lignocaine adequate

for complete motor block during epidural analgesia. On the other hand the 17 ml lignocaine of that strength injected in the present case produced manifest motor paralysis all the way between the injection site at lumbar 3–4 vertebrae and the cervical origins of the phrenic nerve, though it spared the motor nerves to the lower extremity. Such widespread nervous effects could result, in these circumstances, from no other known anatomical pathway than the epidural space.

In order to confirm this point the spinal fluid obtained 75 minutes after injection was chemically analyzed for lignocaine content. Approximately 0.5 mg lignocaine was found in 10 ml of spinal fluid examined, possibly a little less. This is the equivalent of a therapeutic subarachnoid dose of 50 mg lignocaine diluted in 100 ml fluid, as against the 340 mg actually used in this case. While no figures for lignocaine could be found, Frumin et al. (1953) recovered up to 10 per cent of epidural procaine from the spinal fluid, and Frey and Soehring (1955) later pointed out that even a derivative of alkylpolyethelenoxide with large molecules repeatedly administered epidurally to animals could pass into the subarachnoid space in amounts sufficient to effect structural change in intradural roots. The chemical analysis, of course, in indicating spread as such, cannot be regarded as infallible, as a total subarachnoid spinal block can follow even 4 mg amethocaine in patients with a large tumour in the abdomen (Harmel, 1957). The chemical tests nevertheless established that the order of the lignocaine concentration determined was that to be expected in the spinal fluid as a result of diffusion through the intact dura some 75 minutes after epidural injection.

Nishimura, Kitahara and Kusakabe (1959) recently demonstrated the cephalad spread of solutions in the epidural space in the sitting position secondary to the hydrostatic effects of the spinal fluid. Using a Geiger-Mueller counter and injecting 20 ml 2 per cent lignocaine with I-131 they also demonstrated a remarkable tendency towards a cephalad spread in their patients over the age of 50. X-ray examination of the whole spine and pelvis indicated degenerative and oesto-arthritic changes throughout the author's patient in the form of marked narrowing of the intervertebral spaces between C4, 5, and 6 and anterior and posterior lipping of the bodies. A scoliosis and rotation of the lumbar vertebral column was also noticed by the radiologist (Dr. I. A. Brotman). Osteo-arthritis of this type is well known to block the intervertebral foramina and to be accompanied by sparse fatty tissue which is ineffective in limiting the spread of solutions in the epidural space. It is almost certainly for this reason, too, that the common complications of subarachnoid spinal analgesia such as headache are far less common in the elderly (Vandam and Dripps, 1956). Stout (1957), too, noted a greater intensity of epidural block after all the analgesic solutions with increasing age, although lignocaine figured prominently in delayed reactions attributable to late absorption.

From all these considerations it follows that with advancing years the distribution of fluids in the epidural space becomes too unpredictable for clinical usefulness. In view of the unchanging or actually improved applicability of subarachnoid spinal analgesia in patients over 50 years of age it is doubtful whether epidural anaesthesia should ever be employed in those in this age group.

SUMMARY

A case of two consecutive accidental total epidural blocks in the same patient, a 70-year-old diabetic, hypertensive and arthritic male, is described. Subarachnoid extension could be ruled out clinically and was shown to have been unlikely by means of chemical analysis. A review of the relevant factors leads the writer to suggest that epidural blocks should be replaced by a more predictable method such as subarachnoid spinal analgesia in patients over the age of 50 years.

ACKNOWLEDGMENT

Thanks are due to Dr. W. B. Marloth of the Government Chemical Laboratories, Johannesburg, who was responsible for the chemical analysis of the spinal fluid, for time-consuming and stimulating discussion of his findings.

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BOOK REVIEW

Electroencephalography in Anesthesiology. By Albert Faulconer, jr., M.D., M.S., and Reginald G. Bickford, M.B., Ch.B., M.R.C.P. Published by Thomas Books (American Lecture Series). Pp. 90. Price 38*s*.

We live in a period in the history of anaesthesia which may well be remembered as characterized principally by the development of monitoring techniques. We are passing through an era of what is frequently referred to as "instrumentation in anaesthesia." There are probably few who would deny that accurate observation of changes in heart rhythm, blood gases and electrolytes will provide, and is in fact providing, to the investigator useful information upon which he may base suggestion for improvements in technique. Investigational monitoring in this way is contributing significantly to the greater comfort and safety of our patients. Many, however, may wonder whether "instrumentation in anaesthesia" will, if allowed to get out of hand, direct the clinician's attention away from his patient and towards his fascinating electronic equipment.

Be that as it may, the book under review is a brief and admirably clear exposition of a facet of monitoring during anaesthesia which has provided interesting, if not vital, information. Much of what the reviewer is trying to say above is summed up in the following quotation from the Introduction:

"We must conclude that electroencephalography is a valuable tool in certain specific applications but that it is no more than a tool in the hands of the clinical anaesthesiologist. Its value must be assessed in relationship to other circumstances peculiar to the moment."

The indications which are given for electroencephalography during anaesthesia can be safely endorsed except inasmuch as two of them suggest that electroencephalography can be depended upon to indicate the maintenance of "a steady state" of anaesthesia. This is very open to question. The only "steady state" it indicates is that of the electroencephalograph.

Finally there will be few British anaesthetists who will feel sympathy with the concept of "Servoanaesthesia" described in the final chapter of the book. Changes in the electroencephalograph may be geared to control automatically the administration of the anaesthetic, but this surely is just an interesting gimmick. It may possibly be a useful laboratory technique for certain experiments, but certainly, for the many reasons which are well known, it is quite unsuitable for clinical application.

Cecil Gray

Brit. J. Anaesth. (1960), 32, 616

AN INFLATING SPILL VALVE FOR CONTROLLED RESPIRATION IN A SEMICLOSED CIRCUIT

BY

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Medical Section, The Commonwealth Industrial Gases Limited, Sydney, Australia

ONE of the main problems in a semiclosed circuit is the disposal of excess gases. When the patient's lungs are manually inflated, this difficulty is usually overcome by intermittently opening an expiratory valve or by inflating against a fixed leak. When a mechanical ventilator is used the operation of the machine itself may be disturbed by the increase in mean pressure in the circuit which occurs unless there is a "spill" to deal with the continuously increasing volume of gases (Mushin et al., 1959).

To overcome this problem we have introduced a valve which is similar to that described by Steen and Lee (1960). As will be seen it differs from Steen and Lee's valve in that it is possible to adjust the distance between the seat faces by screwing them together or apart. This is important for this means the amount of "spill" can be adjusted to the varying gas flows into the circuit. It consists of a lightly spring-loaded disc situated between two seat faces (fig. 1). Any pressure due to excess gases lifts the disc and these pass freely to atmosphere (fig. 1 (i)).

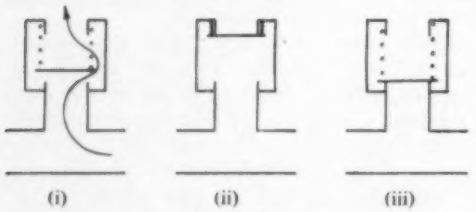

FIG. 1

Diagrams illustrating the principle of the valve:
(i) Excess gases lifting the disc and passing to atmosphere.
(ii) Inflation. The disc seals against the upper seat face.
(iii) Commencement of negative or resting phase. The disc closes against the lower seat face.

At the commencement of inflation the pressure in the circuit rises rapidly due to squeezing of the bag or compression of the ventilator bellows. The disc then flips up to the position shown (fig. 1 (ii)) and closes the circuit from the atmosphere so that full lung inflation is possible.

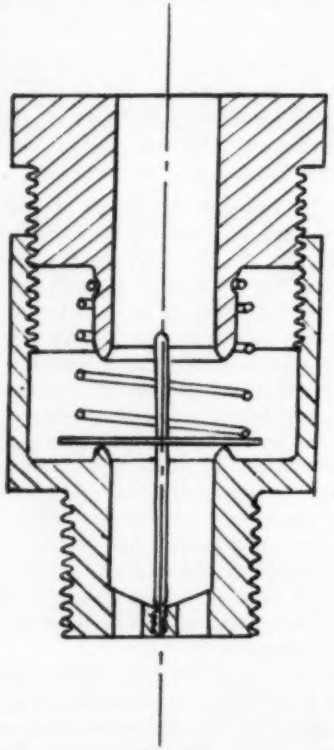

FIG. 2

Cross-section of the valve.

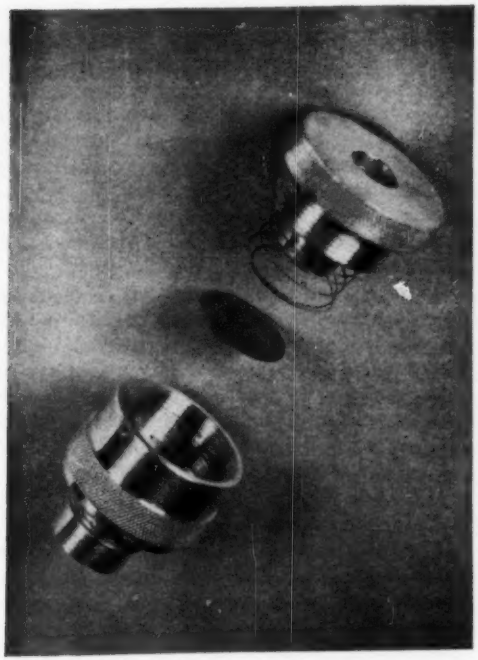

FIG. 3
The components of the valve.

FIG. 4
The valve in use on the Boyle's Machine.

At the end of the inspiratory phase, when the hand pressure is released or the ventilator mechanism trips, the disc returns to the resting position (fig. 1 (iii)). If a negative expiratory phase is provided the disc remains against the lower seat face until excess gases lift it gently when this phase ends.

The appearance and structure of the valve can be seen in figures 2, 3 and 4. It is mechanically simple and moisture does not cause sticking of the disc.

When manually inflating, "spills" may, if desired, be effected consciously by gentle squeezing of the bag sufficiently to lift the disc, but not to seal it against the upper seat face. However, there is another feature; during the rapid travel of the disc on normal inflation some gas must escape as the disc moves from one seat face to the other. In practice the valve has been designed so that the amount of this spill can be adjusted by varying the distance between the seat faces (figs. 2 and 3). Thus it is possible to adjust this position so that the amount spilled in this manner equals the amount of fresh gases added to the circuit and the volume in the circuit can therefore be kept constant without repeated manipulation. As opposed to a "fixed leak", this introduces an "intermittent leak" into the circuit and when the valve closes after spilling in this manner the anaesthetist can accurately feel the degree of lung inflation.

Ideal inflating curves show a fall to zero pressure in the resting phase (Cournand et al., 1958). With the valve in use, if manual pressure on the bag is maintained after inflation, the disc will remain in the "up" position, ultimately locking there if the bag becomes over-distended. Early release of the pressure on the bag will prevent this. Thus the valve efficiently detects the fault in technique of not allowing circuit pressures to return to near-zero levels.

When a mechanical ventilator is used in a semi-closed circuit the effect of an inadequate "spill"

will be determined by whether the ventilator is pressure or volume cycled.

In pressure-cycled ventilators the pressure at which the mechanism trips marking the end of the inspiratory phase is fixed for a given machine and continuous increase in retained volume of gases causes a diminishing pressure difference between resting and peak pressure values. This results in (*a*) a rise in mean intrapulmonary pressure and (*b*) a diminishing exchange of gases per cycle.

In volume-cycled machines the end-inspiratory peak pressure rises steadily with each cycle as fresh gases are added. A constant volume is being delivered but at a rising pressure. At a certain point the pressure limit of the safety valve of the machine is reached and a percentage of the delivered volume goes now, not to the patient but to atmosphere. Again we have: (*a*) a rise in mean intrapulmonary pressure and (*b*) diminished exchange of gases per cycle.

These effects are shown diagrammatically in figures 5 and 6.

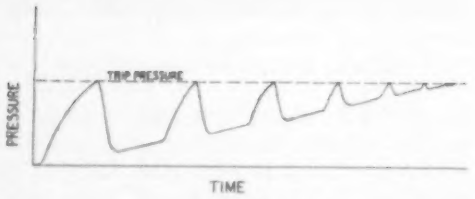

FIG. 5

Diagrammatic representation of the operation of a pressure-cycled ventilator in a closed circuit with more-than-basal fresh gas supply.

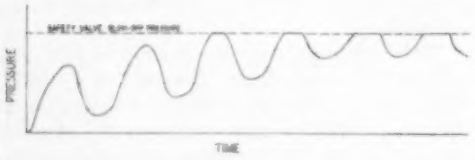

FIG. 6

Diagrammatic representation of the operation of a volume-cycled ventilator in a closed circuit with more-than-basal fresh gas supply.

Most mechanical ventilators at present in use have no provision for effective disposal of gases in excess of basal requirements. The use of the valve described solves this problem.

It is possible that the circuit might be rapidly filled (e.g. from the emergency oxygen supply) creating a positive pressure in the circuit, causing the valve to lock in the "up" position. Under these circumstances the pressure can be released by opening the circuit by the usual methods, but in practice this is an uncommon event.

The valve can be easily placed to discharge excess gases immediately before passing through the soda lime. With most other expiratory valves this situation, although theoretically ideal, is inconvenient for constant manipulation; however, constant manipulation is not required with this valve.

SUMMARY

A valve is described whose features are:

It permits inflation of a patient in a semiclosed circuit without pressure build-up due to excess gases.

If adjusted properly it enables the volume of gases in the circuit to be maintained at a relatively constant level without constant manipulation.

It is mechanically simple, robust, sterilizable and electrically conductive.

There is no pressure build-up in the circuit if the anaesthetist lays the inflating bag aside temporarily while performing some manipulation.

It detects the fault in technique of not allowing circuit pressure to return to near-zero after inflation.

The valve can conveniently be situated in the circuit before the soda-lime canister.

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BERNARD JOHNSON MEMORIAL

Sir,—An appeal for funds to set up a memorial to Bernard Johnson was launched last March. It was hoped at that time to raise the sum of £6,000, which would cover the cost of a memorial plaque to be placed in the Research Laboratories of the Faculty and to endow the salary of the Faculty Adviser in Postgraduate Studies. To date approximately £3,000 has been raised, which falls some way short of the minimum required for this endowment.

An anonymous donor has most generously offered to match any further donations received before March 27, 1961, when the fund will be closed. Should any of your readers wish to subscribe, or to add to their previous donations, their contributions should be addressed to me at the Faculty of Anaesthetists, Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2.

GEOFFREY ORGANE,
Dean, Faculty of Anaesthetists,
Royal College of Surgeons.

VOMITING AND HEAD-UP POSITION

Sir,—We regret that circumstances have delayed a reply to Dr. Sykes (1960), who comments on our work previously published (Hodges et al., 1959), relating to the safety of the head-up position for induction of anaesthesia.

On the question raised in the last paragraph we can offer some real and positive evidence. Dr. Sykes questions the real safety of the technique and wonders whether it is "merely due to sleight of hand". We are flattered, but we cannot agree that the particular skill of a few experienced anaesthetists plays any major part in the real safety of the method. Dr. Sykes suggests that our technique can only be regarded as the technique of choice when it has been practicable in use by "those who would commonly use the technique, that is to say registrars in busy hospitals. . . ." In this group all our registrars and senior house officers circulate through every department, each completing a six months' turn in the Obstetric Anaesthetic Unit usually in the later stages of their appointment. After a period of training and *when they have become experienced* practice has proved them perfectly competent to use this method. In the past four years many junior anaesthetists have completed a period of training in this manner and the thiopentone suxamethonium head-up induction technique has been adopted for all anaesthetics in our very busy obstetric unit. We have now completed 1,500 cases. In the last three years over 80 per cent of the anaesthetics have been administered by our "experienced juniors." A fuller report of these cases has been given elsewhere (Hodges, 1960).

We consider the rapid intravenous injection of thiopentone and suxamethonium in the head-up position to be the safest way to ensure a rapid and safe induction and intubation. With regard to the hypotensive effects of the thiopentone, we can only say that in these 1,500 inductions for obstetric operative procedures we have never been worried clinically by such signs. In the majority of our cases, however, the patients legs were flexed with the knees bent, as well demonstrated in the published photograph (Hodges et al., 1959).

We consider this technique superior to suxamethonium combined with cyclopropane, or other inhalational methods, when planned rapid intubation is to be performed. We would draw attention to a recent report on maternal deaths (Walker et al., 1960) which states (when dealing with the anaesthetic aspects of maternal mortality), "It is striking that in ten cases tracheal intubation does not appear to have been planned. . . . Although in seven cases vomiting and regurgitation occurred before intubation could be completed, it is likely that more widespread use of tracheal intubation has avoided many fatalities through this cause. . . . these tragedies could have been avoided by a more experienced anaesthetist."

The report further states "A consultant anaesthetist should be responsible for anaesthesia in the obstetric department, for the instruction of his juniors, and should be available for consultation by them in any case of difficulty." We have proved the value of this policy in practice. We do not feel that any anaesthetist inexperienced in the particular requirements and hazards of emergency obstetric anaesthesia would be competent

to undertake such cases with safety; but we take steps to see that this does not occur. We agree that intragastric pressures may occur in some cases greater than can be counterbalanced by a 40 degree head-up tilt. For this very reason we certainly have not abandoned altogether the use of pre-operative gastric aspiration in those cases where it is strongly indicated. However, in our unit in over 1,500 obstetric anaesthetics the anaesthetists concerned have considered the passage of a stomach tube pre-operatively to be necessary in less than 1 per cent of cases.

As always no technique, however carefully conceived, can produce 100 per cent protection against all possible hazards and we do not claim that, in this respect, our technique is exceptional. However, we can claim that over a period of 4 years and in 1,500 patients the technique has proved to be efficient and safe, and has been competently handled by a succession of trainee juniors to whom we, and the obstetric department as a whole, are very grateful.

Dr. Sykes states that "a true assessment of the safety of a technique can only be achieved by studying a series of cases under properly controlled conditions . . . after a decision has been made regarding the risks of aspiration."

We stress that our remarks are based on clinical observations gained during practical experience and not in experimental studies. Furthermore, we write primarily of emergency obstetric anaesthesia. We feel that our series was properly controlled in so far as clinical conditions allowed. We also feel that each individual "aspiration risk" is too difficult to assess with accuracy; furthermore we are not prepared to risk our patients with techniques alternative to that which we believe has shown itself to be in the best interests of mother and baby.

R. J. HAMER HODGES
M. E. TUNSTALL
J. R. BENNETT
(Portsmouth)

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HALOTHANE IN THE CLOSED CIRCUIT

Sir,—I should like to congratulate Prof. Mushin and his co-workers on their enterprising and laborious study of "The Concentrations of Anaesthetics in Closed Circuits" (*Brit. J. Anaesth.*, 1960, **32**, 298–333). I regret that I must deplore their conclusions (page 333). I agree that an anaesthetist "should understand clearly the way in which alveolar concentrations . . . [are] dependent on the factors of ventilation, fresh-gas flow, and vaporizer characteristics". But I doubt very much whether many anaesthetists have the mathematical facility of Prof. Mushin's useful assistant; whereas they can quite properly be expected to recognize when a known concentration of an agent is producing more than the expected effect. I suggest that the fact that patients vary in their response to a known concentration of an agent is no argument in favour of the vaporizer in circuit (v.i.c.) system as this merely adds more variables.

As regards the "built-in" safety factor of the v.i.c. system, I personally, first heard this proposed many years ago by an anaesthetist of the old school in respect to open-drop chloroform. I was not convinced by this argument then and am still less so now when so much more is known about the deleterious effects of high P_{CO_2} levels in association with potent volatile anaesthetics.

I have no wish to make rules and regulations but I suggest that the following rules are worth considering.

(1) Halothane should not be given except by, or under the direct supervision of, a competent anaesthetist.

(2) The vaporizer outside the circuit (v.o.c.) system should always be used, with an efficient flow and temperature-compensated vaporizer:

(3) An anaesthetist should never feel precluded from aiding or controlling respiration.

(4) The economy possible with low-flow systems is not to be weighed in the balance with safety.

R. CECIL BROWN,
Bethesda, U.S.A.

Sir,—Dr. Brown has mistaken the purpose of the three papers on "The Concentration of Anaesthetics in Closed Circuits" by ourselves and our colleague W. W. Mapleson, Ph.D., in your issue of July 1960. It was not to make rules but to expose the truth.

In considering the impact of our theoretical and experimental findings on the clinical use of halothane in a closed circuit, the pros and cons of both the v.i.c. and v.o.c. systems were discussed without advocacy of one rather than the other. Anaesthetists are now possessed of the basic knowledge regarding the factors which determine the inspired vapour concentration in both these closed circuit arrangements, and it is up to them, not us, which type of circuit they use in any particular circumstances. If they choose the v.i.c. and the patient is breathing spontaneously, then the latter's life is in *some* degree safeguarded by his ventilation becoming shallower as anaesthesia deepens. To that extent, there is a "built-in safety factor" in the v.i.c. arrangement *only so long as spontaneous breathing is present.*

The conclusions we reached in our paper were clearly set out and in case Dr. Brown is not alone in missing their import we give them again:

> "It is apparent that each circuit has its own advantages and disadvantages. It must be left to the individual anaesthetist to decide which is better suited to the particular circumstances of his own clinical practice. A minimum requirement, however, is that he should understand clearly the way in which the alveolar concentration and hence the depth of anaesthesia is dependent on the factors of ventilation, fresh-gas flow, and vaporizer characteristics.
>
> "It seems to us that in the hands of an experienced anaesthetist either arrangement is equally safe (or unsafe). If the anaesthetist is less experienced with potent anaesthetics such as halothane, he is better advised to use a calibrated and preferably thermostatically controlled vaporizer placed outside the breathing circuit, especially if he intends to assist or control the respiration. By this means the somewhat unpredictable effects in the v.i.c. system of alterations in the patient's ventilation on the inspired concentration of anaesthetic are avoided, particularly if controlled respiration is performed."

There is therefore little disagreement between our views and those of Dr. Brown. He need, however, have no hesitation in making rules if only they were condensed into one, i.e., that no anaesthetist should administer potent vapours from a closed circuit unless he understands clearly the way in which alveolar ventilation is dependent on the factors of total ventilation, fresh-gas flow, and vaporizer characteristics. Any other rules are superfluous.

WILLIAM W. MUSHIN
S. GALLOON
Cardiff

HALOTHANE IN CLOSED CIRCUIT WITH GOLDMAN VAPORIZER

Sir,—Please allow us to comment on the article on p. 388 of your August issue (Gusterson and Clark, 1960). The statement that the use of halothane in the ether vaporizer of the C.M. or circle unit is not satisfactory is at variance with the facts. We have records of more than 6,000 anaesthetics so administered and have encountered no difficulties or dangers due to the method.

Figure 3 on p. 389 purports to show halothane concentration obtained using our method. In the first or left-hand half of the graph a total gas flow of 3 litres per minute was used, which is a technique we have never described. Furthermore the vaporizer control is turned to "full on" at one point. We have never advised a vaporizer setting of more than "¾ on" when using the C.M. unit. The second half of the graph more fairly portrays our method. The increase in halothane concentration to more than 5 per cent V/V when the vaporizer control was turned to mark 3 was to be expected, as was the automatic fall to 3 per cent V/V as the minute volume fell due to respiratory depression. This built-in safety factor has been demonstrated by ourselves, Marrett (1957) and Mushin and Galloon (1960). We do not regard a concentration of 5 per cent V/V as in itself dangerous though it is clinically unnecessary in the majority of cases.

We contend that, given reasonable care, any closed circuit vaporizer designed for use with ether is suitable for halothane administration provided it is purely a surface vaporizer (i.e. not including wicks or the bubbling of basal gas

through the halothane). The essential point is to observe the physical signs of anaesthesia and adjust the vaporizer accordingly. More than three years of experience has not caused us to modify the technique we originally described (Brown and Woods, 1958a) except that we now adjust the basal flow of oxygen to requirements of the individual case, instead of using a standard 500-ml flow.

We would also like to remind anaesthetists wishing to use C.M. units for closed circuit halothane anaesthesia that the standard washers should be replaced by a special plastic set which can be obtained from the British Oxygen Company, Ltd. and if necessary fitted by their service engineer (Brown and Woods, 1958b). Modification of C.M. units to a true circle absorber should be effected as described recently (Brown and Woods, 1960).

M. A. WOODS,
T. A. BROWN,
Ards Hospital, Newtownards, N. Ireland.

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Sirs,—We accept the statement of Woods and Brown that in their hands the method they describe of using halothane in the ether canister of a Coxeter-Mushin absorber unit is "satisfactory". We feel, however, that a method which has such potential dangers cannot be accepted by the majority of anaesthetists. The purpose of the graph in figure 3 of our paper was to demonstrate some of these dangers.

There are now very few Coxeter-Mushin absorber units in use, and as they themselves now admit these units must be modified to a true circle unit before use with the low minute volumes obtained with halothane. The ether canister of the modern Boyle type II absorber unit is not graduated at $\frac{1}{4}$, so that confusion must arise in those using their method with a modern machine. We wish to stress that with the Goldman vaporizer there is never any danger of gross overdosage, provided the patient is breathing spontaneously.

The actual flow rate of the input gases is not the main factor in determining the percentage of halothane breathed by the patient, but rather the patient's minute volume. We feel it unwise to depress this minute volume by a high concentration of halothane even when breathed for a few breaths, particularly as our graph shows that at one time the minute volume fell from 5 litres a minute to 2.5 litres a minute with no appreciable alteration in the halothane concentration.

We have always stressed that the control of a halothane anaesthesia must always be the clinical condition of the patient; but is it exercising "reasonable care" to use a vaporizer which is capable of giving lethal concentrations of halothane now that a much simpler and safer apparatus is available?

F. R. GUSTERSON,
J. M. CLARK,
Worthing Group Hospitals

A TRUE CIRCLE CONVERSION OF THE "C-M" ABSORBER UNIT

Sir,—Drs. T. A. Brown and M. A. Woods (*Brit. J. Anaesth.*, **32**, 338) have shown ingenuity in modifying the soda lime canister of the "C-M" absorber unit so that it could be used on the exhalation side of the circle absorber.

There are two alternatives which I think are worth trying. One is to modify two canisters and place one on the inhalation side and one on the exhalation side, thus creating a "two-canister true circle" arrangement. This would give a performance about four times greater than that of a single canister. The other alternative is to place an unmodified canister of soda lime in the usual place and fit the modified canister on the inhalation side. This would give a performance slightly less than the "two-canister true circle" arrangement but a good deal better than the one-canister "true circle".

W. H. J. COLE,
Melbourne

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